UNITED STATES DISTRICT COURT
NORTHERN DISTRICT OF OHIO
WESTERN DIVISION

IN RE:	)	**CASE NO. 1:08HC60000**
	)	**MDL NO. 1953**
HEPARIN PRODUCTS	)	
LIABILITY LITIGATION	)	**Judge James G. Carr**
	)	
	)	**MEMORANDUM OF OPINION**
	)	**AND ORDER**

This multi-district products liability litigation arises out of the manufacture and sale by defendants of contaminated heparin. The plaintiffs allege that the use of contaminated heparin caused a myriad of adverse reactions leading to serious injuries and, in some cases, death.

Pending is defendants' motion for summary judgment on the following categories of claims:

- Claims lacking evidence of any symptoms within sixty minutes of heparin administration;
- Claims alleging heparin-induced thrombocytopenia (HIT);
- Claims alleging sepsis or sepsis-like conditions;
- Claims alleging bleeding or clotting;
- Claims alleging injury due to administration of non-bolus doses of contaminated heparin;
- Claims alleging exposure to contaminated heparin containing less than 15% of the contaminant Oversulfated Chondroitin Sulfate (OSCS); and
- Claims falling outside the CDC case definition.

[Doc. 527].

Also pending are several *Daubert* challenges ancillary to the summary judgment motion. Defendants have filed a motion for exclusion of general causation testimony by plaintiffs' experts Drs. Hoppensteadt, Jeske, Kiss, Buncher, Luke and Ohr [Doc. 528]. Plaintiffs have filed motions for exclusion of the testimony of Dr. Howard William Ory [Doc. 438] and Dr. Ronald M. Burch [Doc. 442]. I also take notice of plaintiffs' motion, which became decisional as this order was being completed, for an order to show cause relating to the licensing and board certification of Dr. Burch. [Doc. 583].

For the reasons that follow, I grant in part and deny in part the parties' *Daubert* motions. I grant in part and deny in part defendants' motion for summary judgment.

Background

A. Heparin Contamination

Heparin, one of the oldest clinical drugs still in wide-spread use, has been marketed in the United States for nearly seventy years. Over one million multi-dose vials of heparin are sold per month in the United States. Baxter Healthcare Corporation (Baxter) supplies about half the heparin sold in the United States.

An anticoagulant, heparin decreases the clotting ability of blood, thereby preventing formation of clots and stopping the growth of already existing clots. Heparin is used as a prophylaxis against blood clots among bed-ridden hospital patients, as an anticoagulant during surgeries and in catheters and pumps during procedures such as kidney dialysis, and as a treatment of such conditions as pulmonary embolism and deep-vein thrombosis.

Many patients who receive heparin have serious pre-existing medical conditions. Patients with end-stage renal disease and patients undergoing coronary artery bypass surgery make up a significant number of those receiving vial heparin.

To survive, patients with end-stage renal disease must undergo dialysis or receive a kidney transplant. There are two forms of dialysis: hemodialysis, in which a machine filters wastes, salts and fluid from the blood, and peritoneal dialysis, in which dialysate is washed in and out of the peritoneal cavity. Heparin is incorporated into both therapies.

Even when receiving dialysis, end-stage renal disease patients suffer a significant background mortality rate. Dialysis patients also commonly experience side effects such as drop in blood pressure, shortness of breath, abdominal cramps, nausea and vomiting.

A coronary artery bypass graft is an open-heart procedure that involves grafting a new artery or vein around diseased or blocked sections of the arteries in order to increase blood flow to the heart muscle tissue. A bolus dose of heparin is often administered at the outset of the procedure. Coronary artery bypass graft patients may experience side effects including drops in blood pressure and platelet counts. Complications include heart failure, heart attacks, serious arrhythmia, stroke and respiratory, renal and multiple organ failure.

Heparin is generally well-tolerated. Although laboratory monitoring is necessary to ensure its therapeutic effect and safety, it has predictable pharmacokinetics.

The most common adverse event related to heparin administration is bleeding, which is variable in severity. Serious bleeding occurs with a reported frequency of 1–3%. Heparin-induced thrombocytopenia (HIT) is another serious complication of heparin therapy. HIT is the development of thrombocytopenia (a low platelet count) associated with the administration of heparin.

When a person suffers from HIT, the immune system forms antibodies against heparin. These antibodies are bound to a protein called platelet factor 4 (PF4) and usually develop between four and fourteen days after initial exposure to heparin. HIT predisposes a patient to thrombosis, the abnormal formation of blood clots in a blood vessel. Immune-mediated HIT is a potentially life-threatening complication occurring in 1–2% of patients receiving unfractionated heparin. Hypersensitivity and allergic-type reactions are rare.

In late December, 2007, the U.S. Food and Drug Administration (FDA) and Baxter received over 350 adverse event reports associated with the use of heparin. The FDA characterized this as a marked increase from the usual number of reports associated with heparin use. This led to investigations by the U.S. Centers for Disease Control and Prevention (CDC) beginning in January, 2008.

The CDC identified a cluster of symptoms based upon initial reports of allergic-type reactions among pediatric hemodialysis patients. After the CDC solicited further reports of similar reactions among hemodialysis patients, the agency identified Baxter heparin as a common feature among the reported cases. On January 17, 2008, Baxter recalled nine multi-dose lots, and on February 29, 2008, Baxter recalled all its heparin single and multi-dose vials and HEP–LOCK flush products.

Intense efforts to determine the nature and source of the contaminant followed. On March 19, 2008, the FDA announced that the active pharmaceutical ingredient (API) in Baxter's heparin had been intentionally contaminated with Over-Sulfated Chondroitin Sulfate (OSCS). OSCS is a synthetic compound with anticoagulant properties mimicking those of heparin. Baxter obtained this

contaminated API from its Chinese supplier, defendant Scientific Protein Laboratories (SPL), and incorporated it into some of its heparin products.

B. Retrospective Studies

In December, 2008, researchers with the CDC's Epidemic Intelligence Service and others published a retrospective study of reported adverse event data using a facility-based case-control methodology (the Blossom Study).[1] This study resulted from the CDC's January, 2008, investigation of the severe adverse reactions associated with heparin reported between November, 2007, and January, 2008.

Preliminary findings suggested that heparin was a possible cause of the reactions. Seeking to identify the source of the outbreak of adverse events, the CDC investigation began collecting information about adverse events and identifying control facilities (those facilities reporting no reactions).

For this investigation, the CDC defined a definite case of adverse reaction as the sudden onset of angioedema (i.e., facial swelling) or urticaria (hives) in a patient within one hour of heparin administration. It defined a probable case as the development, also within one hour of heparin administration, of hypotension, loss of consciousness, or signs and symptoms from at least two of the following categories: sensation of burning, warmth, or flushing; numbness or tingling; difficulty swallowing; shortness of breath, audible wheezing, or chest tightness; tachycardia; and nausea, vomiting, or diarrhea.

[1] David B. Blossom, *et al.*, *Outbreak of Adverse Event Reactions Associated with Contaminated Heparin*, 359 New Eng. J. Med. 2674 (2008).

The researchers found that the adverse reactions were most often characterized by hypotension, nausea, and shortness of breath occurring within thirty minutes of administration, with a mean time to reaction of 5.1 minutes during dialysis and 15.9 minutes during cardiac treatments. The researchers observed that similar adverse reactions had been documented in the past among hemodialysis patients. Those reactions had been attributed to a variety of different causes, including dialyzer membranes, water impurities, residual disinfectants and medications. Heparin alone, however, rarely causes the symptoms observed.

The Blossom study concluded that "[h]eparin contaminated with OSCS was epidemiologically linked to adverse reactions in [the] nationwide outbreak," and "[t]he reported clinical features of many of the cases further support the conclusion that [OSCS contaminated heparin] was the cause of the outbreak." Use of heparin manufactured by Baxter Healthcare was the factor most strongly associated with reactions.

The Blossom study researchers made no determination of a causal relationship between deaths reported to the CDC and heparin administration. They noted that many deaths occurred among patients suffering from life-threatening diseases. The researchers also cautioned that the cases described likely did not encompass all cases of adverse reactions to contaminated heparin.

The Blossom study included analytic and *in vitro* testing of contaminated heparin vials received from surveyed facilities. These tests confirmed the findings of an earlier animal study that OSCS activates the kinin-kallikrein biological pathway in human plasma.

The kinin-kallikrein system plays a role in inflammation, blood pressure control, coagulation and pain. Activation of the kinin-kallikrein pathways in human plasma generates bradykinin, a

potent vasoactive mediator that causes blood vessels to dilate, thereby lowering blood pressure. Activation of these systems can potentially result in adverse reactions.[2]

Researchers at the FDA's Office of Surveillance and Epidemiology published a second retrospective review in 2010 (the McMahon study).[3] The purpose of the McMahon study was "to describe associations, patterns or signals among allergic-type heparin-associated [adverse events] that may not have been apparent in the more circumscribed sample previously investigated [*i.e.*, the Blossom study]."[4] In considering the adverse event reports, the McMahon study abandoned the symptomatology and sixty minute restriction of the Blossom study, but it limited its focus to anaphylactoid-type reactions. The study concluded that "the mechanism of OSCS kallikrein activation fits the observed events and thus provides biological plausibility to OSCS mediated [adverse events]."

C. Procedural History

Litigation in both state and federal courts followed the contamination crisis. On June 6, 2008, the Judicial Panel on Multidistrict Litigation transferred federal heparin products liability cases to this court for consolidated pretrial proceedings.

Together with the parties, I determined that the best way to proceed was by bellwether trial process. The initial group of bellwether cases were selected based upon the case definition outlined by the CDC in the Blossom study.

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[2] *Id.* (citing Takashi Kei Kishimoto, Ph.D., *et al.*, *Contaminated Heparin Associated with Adverse Clinical Events and Activation of the Contact System*, 358 New Eng. J. Med. 2457 (2008)).

[3] Ann W. McMahon, *et al.*, *Description of Hypersensitivity Adverse Events Following Administration of Heparin That Was Potentially Contaminated with Oversulfated Condroitin Sulfate in Early 2008*, 19 Pharmacoepidemiology & Drug Safety 921 (2010).

[4] *Id.* at 928.

The pending summary judgment motion seeks dismissal of claims of injury or death where the allegedly causative reactions are outside the CDC case definition parameters. These reactions include HIT, bleeding or clotting, sepsis, injuries with a time to onset greater than one hour after administration of contaminated heparin, and injuries involving non-bolus dosing or subcutaneous administration rather than intravenous administration. The defendants also seek summary judgment with regard to claims alleging exposure to contaminated heparin containing less than 15% OSCS.

In addition to reviewing the parties' briefs and the numerous exhibits, I held a two-day *Daubert* hearing addressing the testimony of plaintiffs' experts Dr. Debra Hoppensteadt and Dr. Joseph Kiss and defendants' expert Dr. Ronald M. Burch. On the basis of this testimony and the record, I am now prepared to rule on the instant motions.

Standard of Review

A party is entitled to summary judgment on motion under Federal Rule of Civil Procedure 56 where the opposing party fails to show the existence of an essential element for which that party bears the burden of proof. *Celotex Corp. v. Cartrett*, 477 U.S. 317, 322 (1986). The movant must initially show the absence of a genuine issue of material fact. *Id.* at 323.

Once the movant meets that initial burden, the "burden shifts to the nonmoving party [to] set forth specific facts showing there is a genuine issue for trial." *Anderson v. Liberty Lobby, Inc.*, 477 U.S. 242, 250 (1986) (quoting Fed. R. Civ. P. 56(e)). Rule 56(e) "requires the nonmoving party to go beyond the [unverified] pleadings" and submit admissible evidence supporting its position. *Celotex, supra*, 477 U.S. at 324.

In deciding a motion for summary judgment, I accept the opponent's evidence as true and construe all evidence in the opponent's favor. *Eastman Kodak Co. v. Image Tech. Servs., Inc.*, 504

U.S. 451, 456 (1992). The movant can prevail only if the materials offered in support of the motion show there is no genuine issue of a material fact. *Celotex*, *supra*, 477 U.S. at 323. An issue is "genuine . . . if the evidence is such that a reasonable party could return a verdict for the nonmoving party." *Anderson*, *supra*, 477 U.S. at 248.

Discussion

Baxter moves for summary judgment on seven categories of claims, arguing that plaintiffs have failed to set forth admissible evidence that contaminated heparin can cause the injuries asserted in these categories of claims.

The parties agree that plaintiffs must present evidence of both general and specific causation to prevail on their claims. "General causation is established by demonstrating, often through a review of scientific and medical literature that exposure to a substance *can cause* a particular disease[,]" while specific causation "is established by demonstrating that a given exposure *is the cause* of an individual's disease[.]" Federal Judicial Center, Reference Manual on Scientific Evidence 444 (2d ed. 2000) (emphasis added); *see also In re Meridia Prods. Liab. Lit.*, 328 F. Supp. 2d 791, 798 (N.D. Ohio 2004) (citing *Sterling v. Velsicol Chem. Corp.*, 855 F.2d 1188 (6th Cir. 1988)). Thus, plaintiffs must present expert testimony to show by a preponderance of the evidence that exposure to contaminated heparin can and did cause plaintiffs' injuries. *See, e.g., Glaser v. Thompson Med. Co.*, 32 F.3d 969 (6th Cir. 1994).

General causation is a critical threshold issue with respect to each claim. Absent credible and scientifically reliable proof of causation, plaintiffs can have no claim against defendants. *E.g., Hisrich v. Volvo Cars of N. Am, Inc.*, 226 F.3d 445, 450, 454 (6th Cir. 2000); *In re Meridia Prods. Liab. Litig.*, 328 F. Supp. 2d 791, 798 (N.D. Ohio 2004), *aff'd*, *Meridia Prod. Liab. Litig. v. Abbott*

Labs., 447 F.3d 861, 868 (6th Cir. 2006) ("[A] plaintiff must show that the substance to which she was exposed *can cause* the type of injury alleged.").

Defendants' motion for summary judgment alleges, *inter alia*, that plaintiffs cannot create a genuine issue of material fact because the testimony of their experts is inadmissible under Federal Rule of Evidence 702. I therefore must address the various *Daubert* challenges in order to determine whether plaintiffs have advanced credible and scientifically reliable proof of general causation. In considering the challenges to the experts and the evidence, I consider the *admissibility* of the evidence. I consider the *sufficiency* of this evidence in addressing defendants' motion for summary judgment. *See Anderson*, *supra*, 477 U.S. at 252.

A. *Daubert* Challenges

Federal Rule of Evidence 702 requires me to perform a "gate-keeping role" when considering the admissibility of expert testimony. *Daubert v. Merrell Dow Pharmaceuticals, Inc.*, 509 U.S. 579, 597 (1993). Rule 702 provides:

> If scientific, technical, or other specialized knowledge will assist the trier of fact to understand the evidence or to determine a fact in issue, a witness qualified as an expert by knowledge, skill, experience, training, or education, may testify thereto in the form of an opinion or otherwise, if (1) the testimony is based upon sufficient facts or data, (2) the testimony is the product of reliable principles and methods, and (3) the witness has applied the principles and methods reliably to the facts of the case.

Rule 702 applies not only to scientific testimony, but also to other types of expert testimony based on technical or other specialized knowledge. *See Kumho Tire Co., Ltd. v. Carmichael*, 526 U.S. 137, 147, 149 (1999).

My gate-keeping function here is three-fold.

First, I must determine whether the witness is qualified as an expert. "When making a preliminary finding regarding an expert's qualifications under Fed. R. Evid. 104(a), the court is to examine 'not the qualifications of a witness in the abstract, but whether those qualifications provide a foundation for a witness to answer a specific question.'" *Smelser v. Norfold Southern Ry. Co.*, 105 F.3d 299, 303 (6th Cir. 1997) (quoting *Berry v. City of Detroit*, 25 F.3d 1342, 1351 (6th Cir. 1994)).

Second, I must determine whether the testimony is reliable. *See Daubert*, *supra*, 509 U.S. at 590. The Court in *Daubert* listed several factors for consideration in assessing the reliability of scientific testimony, including:

- Whether a "theory or technique . . . can be (and has been) tested";
- Whether it "has been subjected to peer review and publication";
- Whether, in respect to a particular technique, there is a high "known or potential rate of error" and whether there are "standards controlling the technique's operation"; and
- Whether the theory or technique enjoys "general acceptance" within a "relevant scientific community."

Kumho Tire, *supra*, 526 U.S. at 149–50 (quoting *Daubert*, *supra*, 509 U.S. at 592–94).

The test of reliability is, however, "flexible, and *Daubert*'s list of specific factors neither necessarily nor exclusively applies to all experts or in every case." *Id.* at 140. "[W]hether *Daubert*'s specific factors are, or are not, reasonable measures of reliability in a particular case is a matter that the law grants the trial judge broad latitude to determine." *Id.* at 153. The focus must be on the principles and methodologies on which the expert's opinion is based, and not on the merits of the expert's conclusions. *Daubert*, *supra*, 509 U.S. at 594-595 n.12; *United States v. Bonds*, 12 F.3d 540, 556 (6th Cir. 1993) (district courts "are not to be concerned with the reliability of the conclusions generated by valid methods, principles and reasoning.").

Finally, I must determine whether the expert's reasoning or methodology can properly be applied to the facts at issue: *i.e.*, whether the opinion is relevant. *See Daubert*, *supra*, 509 U.S. at 591–93. To be relevant, the testimony must "assist the trier of fact to understand the evidence or to determine a fact in issue." Fed. R. Evid. 702. This relevance requirement ensures that there is a "fit" between the testimony and the issue to be resolved at trial. *United States v. Bonds*, 12 F.3d 540, 555 (6th Cir. 1993).

Rejection of expert testimony "is the exception rather than the rule." *In re Scrap Metal Antitrust Litigation*, 527 F.3d 517, 531 (6th Cir. 2008) (quoting Fed. R. Evid. 702 Advisory Committee's Note, 2000 Amend.). My role as gatekeeper "is not intended to serve as a replacement for the adversary system: '[v]igorous cross-examination, presentation of contrary evidence, and careful instruction on the burden of proof are the traditional and appropriate means of attacking shaky but admissible evidence.'" *U.S. v. 14.38 Acres of Land*, 80 F.3d 1074, 1078 (5th Cir. 1996) (quoting *Daubert*, *supra*, 509 U.S. at 597).

In assessing expert testimony, I "should also be mindful of other applicable rules." *Daubert*, *supra*, 509 U.S. at 595. Federal Rule of Evidence 703 provides that "[i]f the underlying data are so lacking in probative force and reliability that no reasonable expert could base an opinion on them, an opinion which rests entirely upon them must be excluded." *In re Paoli RR. Yard PCB Litig.*, 35 F.3d 717, 748 (quoting *In re "Agent Orange" Prod. Liab. Litig.*, 611 F. Supp. 1223, 1245 (E.D.N.Y. 1985).

The proponent of the evidence has to establish that all of the pertinent admissibility requirements are met by a preponderance of the evidence. *See* Fed. R. Evid. 104(a); *see also Bourjaily v. United States*, 483 U.S. 171, 175–76 (1987).

1. Plaintiffs' Evidence

Defendants assert that I must exclude plaintiffs' evidence because: 1) plaintiffs' experts have "concede[d] that there is no scientific evidence supporting the categories of claims [outside the CDC case definition]; and 2) the evidence on which plaintiffs' experts seek to rely is "insufficient as a matter of law to establish causation." [Doc. 528-1].

Defendants overstate the scope of what plaintiffs' experts "concede." Plaintiffs' experts acknowledge that there are no *epidemiologic studies* showing an increased risk of HIT, bleeding, clotting, sepsis or death. This is not the same as conceding there is no scientific evidence whatsoever supporting the categories of claims outside the CDC case definition.

Defendants also take issue with the fact that plaintiffs' experts often state that contaminated heparin "can" or "may" result in various adverse events, citing Ohio case law requiring an expert to express opinions on proximate cause in terms of probability. *See Soldo v. Sandoz Pharm. Corp.*, 244 F. Supp. 2d 434, 525 (W.D. Pa. 2003) (collecting cases). But plaintiffs' experts do not use the terms "can" or "may" to indicate uncertainty. Rather, this language reflects the fact that the expert opinions here address *general*, as opposed to *specific*, causation. *See Meridia*, 328 F. Supp. 2d at 798.

Defendants argue that *in vitro*, animal and ecologic studies cannot be used to establish general causation, plaintiffs' experts improperly ignore epidemiologic data, and epidemiologic evidence is necessary to prove causation in this case.

a. Non-epidemiological Evidence

Defendants argue that the types of evidence on which plaintiffs' expert rely, which includes *in vitro* studies, *in vivo* animal studies, ecologic studies, adverse event reports, case studies and clinical reports, are insufficient as a matter of law to establish general causation.

Other courts have held otherwise. In their view, the kinds of evidence on which plaintiffs' rely are "all recognized and accepted scientific methodologies, used for assessing the possible side-effects and hazards associated with particular drugs and the causes of disease." *Schott v. I-Flow Corp.*, 696 F. Supp. 2d 898, 905 (S.D. Ohio 2010) (finding general causation experts' opinions based on published and peer reviewed cohort studies, animal studies, and *in vitro* studies reliable where conducting epidemiological studies would be unethical); *McClellan v. I-Flow Corp*., 710 F. Supp. 2d 1092, 1114 (D. Or. 2010) (finding that *in vitro* and animal studies, case series and reports are "routinely reviewed and relied upon by physicians in the normal course of their profession"); *Globetti v. Sandoz Pharm. Corp.*, 111 F. Supp. 2d 1174, 1179 (finding that, in absence of ability to conduct epidemiological studies, animal studies, published medical literature, adverse event reports, medical texts, de-challenge/re-challenge experiment data and case studies presented more than adequate evidence of a scientific nature from which a reliable conclusion could be drawn); *see also*, *Kennedy v. Collagen Corp.*, 161 F.3d 1226, 1229-30 (9th Cir. 1998) (finding peer reviewed articles, clinical trials and product studies, a health department investigation and differential diagnosis sufficient to support causation opinion).[5]

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[5] Although plaintiffs' experts rely on the cumulative evidence available, other courts have recognized the value of *in vitro* studies, animal studies, and case reports individually. *See Bourne ex rel. Bourne v. E.I. Dupont de Nemours & Co., Inc.*, 189 F. Supp. 2d 482, 496 (S.D. W. Va. 2002) ("There can be no dispute that properly designed and conducted animal testing can yield relevant and useful information in the field of human toxicology. Likewise, *in vitro* tests provide useful information about metabolic processes at a cellular level, and may supplement existing animal and human data."); *Caraker v. Sandoz Pharms. Corp.*, 172 F. Supp. 2d 1046, 1050 (S.D. Ill. 2001)

Of course, "[w]hen an expert does not rely on the primary [epidemiological] methodology for establishing causation, then that places a burden on the expert to explain his choice of methodologies." *Meridia*, 328 F. Supp. 2d at 800 (citing *Conde v. Velsicol Chem. Corp.*, 804 F. Supp. 972, 1025-26 (S.D. Ohio 1992). Plaintiffs argue that it would be medically and scientifically unethical to attempt a control-group epidemiological experiment of the effects of OSCS in human beings. To do so would require administering OSCS to patients and exposing them to the possibility of injury.

Nevertheless, plaintiffs must still demonstrate that the reasoning or methodology on which their experts base their opinions is scientifically valid and properly applied to the facts in issue. *Gen. Elec. Co. v. Joiner*, 522 U.S. 136, 144-45 (1997) (holding that animal studies can be a proper foundation for an expert's opinion but that those opinions must be sufficiently supported by the animal studies on which they purport to rely). To this end, when relying on animal, *in vivo* and *in vitro* studies, courts have required experts to "explain how such studies can be reliably extrapolated to prove comparable effects in humans." *In re Prempro Prods. Liab. Litig.*, 738 F. Supp. 2d 887, 894 (E.D. Ark. 2010) (citing *Joiner*, *supra*, 522 U.S. at 144 (1997); *Allison v. McGhan Medical Corp.*, 184 F.3d 1300, 1313-14 (11th Cir.1999); *In re Paoli R.R. Yard PCB Litig.*, 35 F.3d 717, 743 (3d Cir.1994)).

Courts also have expressed skepticism of causation opinions based on solely on adverse event reports, case series, case reports and case studies, but have admitted such opinions when

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("[A]n overwhelming amount of case reports of a temporal proximity between a very specific drug and a very specific adverse event might...be enough to make a general causation conclusion sufficiently reliable."); *see also*, REFERENCE MANUAL ON SCIENTIFIC EVIDENCE, 475 (Fed. Judicial Ctr. Ed., 2d ed. 2002) ("[case reports] may be carefully considered in light of other information available, including toxicological data.").

accompanied by other reliable scientific evidence. *See, e.g.*, *Glaser v. Thompson Med. Co.*, 32 F.3d 969, 972 (6th Cir.1994) (holding that published studies, published articles, case reports, and the expert's own clinical and research experience constituted sufficient reliable scientific data upon which an expert may base conclusion); *In re Phenylpropanolamine Prods. Liab. Litig.*, 289 F.Supp.2d 1230, 1248 (W.D. Wash. 2003).

Because the sum of the evidence on which an expert relies can affect the reliability of the conclusions thereby reached, I will not exclude the evidence on which plaintiffs' experts rely before determining whether they have reached their opinions through a reliable methodology.

b. Failure to Consider Epidemiological Evidence

Defendants assert that I must exclude the testimony of plaintiffs' experts because the epidemiological evidence contradicts the evidence on which plaintiffs' experts rely.

Courts have rejected non-epidemiological evidence as unreliable where there is an overwhelming body of epidemiological evidence to the contrary. *See, e.g.*, *Turpin v. Merrell Dow Pharmaceuticals Inc.*, 736 F. Supp. 737, 743 (E.D. Ky. 1990) (finding *in vitro* studies, *in vivo* animal studies, chemical studies, and human data inadmissible to demonstrate a link between Bendectin and birth defects in light of over thirty epidemiological studies concluding that no statistically significant association existed); *Richardson v. Richardson-Merrell, Inc.*, 857 F.2d 823, 830 (D.C. Cir. 1988) ("Studies of this kind, singly or in combination, are not capable of proving causation in human beings in the face of the overwhelming body of contradictory epidemiological evidence.").

Here, however, there is no such overwhelming body of contrary epidemiological evidence. Defendants point to two epidemiological studies, neither of which were designed to determine whether there was an association between contaminated heparin and any of the conditions identified

in defendants' motion for summary judgment. Absence of proof is not proof of absence, and while these studies do not provide support for plaintiffs' theories, neither do they contradict them. I will not, therefore, exclude plaintiffs' evidence on these grounds.

c. Necessity of Epidemiological Evidence

I decline to categorically exclude plaintiffs' scientific evidence solely on the basis that it is not epidemiological in nature. *Daubert* requires only that the expert's methodology be sound. *Meridia*, 328 F. Supp.2d at 801. As the Sixth Circuit and numerous other courts have made clear, "[n]o requirement exists that a party *must* offer epidemiological evidence to establish causation." *In re Meridia Prods. Liab. Litig.*, 328 F. Supp. 2d 791, 799 (N.D. Ohio 2004).[6] Epidemiological

[6] *See Hardyman v. Norfolk & W. Ry. Co.*, 243 F.3d 255, 261-67 (6th Cir. 2001) (holding that lower court abused its discretion in excluding plaintiff's expert where expert's opinion was based on a differential diagnosis rather than epidemiologic evidence); *Milward v. Acuity Specialty Prods. Grp.*, No. 09-2270, 2011 WL 982385, *10 (1st Cir. March 22, 2011) ("epidemiological studies are not per se required as a condition of admissibility regardless of context."); *Kilpatrick v. Breg, Inc.*, 613 F.3d 1329, 1336-37 (11th Cir. 2010) (holding that absence of epidemiological evidence "not fatal, but makes his task to show general causation more difficult"); *Glastetter v. Novartis Pharm. Corp.*, 252 F.3d 986, 992 (8th Cir. 2002) ("[t]he absence of epidemiological evidence did not doom [plaintiff's] case"); *In re Berg Litig.*, 293 F.3d 1127, 1130 (9th Cir. 2002) ("[n]or is epidemiological evidence the sole method of establishing causation."); *Rider v. Sandoz Pharm. Corp.*, 295 F.3d 1194, 1198 (11th Cir. 2002) (holding that it "is well settled that while epidemiological studies may be powerful evidence of causation, the lack thereof is not fatal to a plaintiff's case"); *Zuchowicz v. United States*, 140 F.3d 381, 385 (2nd Cir. 1999) (affirming the district court's ruling admitting experts' testimony despite lack of epidemiological evidence); *Kennedy v. Collagen Corp.*, 161 F.3d 1226 (9th Cir. 1998) ("it is scientifically permissible to reach a conclusion on causation without" epidemiological or animal studies); *Benedi v. McNeil-P.P.C.*, Inc., 66 F.3d 1378, 1384 (4th Cir. 1995) ("[u]nder the *Daubert* standard, epidemiological studies are not necessarily required to prove causation, as long as the methodology employed by the expert in reaching his or her conclusion is sound."); *Hopkins v. Dow Corning Corp.*, 33 F.3d 1116, 1124-25 (9th Cir. 1994) (affirming district court's decision to allow expert testimony where such testimony was based on scientific data and utilized the types of scientific techniques relied upon by medical experts "in making determinations regarding toxic causation where there is no solid body of epidemiological data to review."); *Ashburn v. Gen. Nutrition Ctrs., Inc.*, 533 F. Supp. 2d 770, 774 (N.D. Ohio 2008) (court did not require epidemiological evidence).

evidence may be the "primary generally accepted methodology for demonstrating a causal relation between [a] chemical compound and a set of symptoms or a disease," but it is not the *only* methodology that scientists use. *Meridia*, *supra*, 328 F. Supp. 2d at 800.

Defendants insist that, while epidemiological evidence is not required to establish causation in *every* case, it is required in *this* case because all of the alleged injuries and diseases can occur in the absence of contamination.

As plaintiffs point out, the court in *Meridia*, *supra*, 328 F. Supp. 2d at 799–800, rejected this rationale.

Plaintiffs in *Meridia* alleged that Meridia, a diet drug, caused cardiovascular injuries. Defendants moved for summary judgment on general causation arguing that the obese population using Meridia suffer from increased risk of cardiovascular conditions, and unless epidemiological studies show this risk increases with Meridia ingestion, there was no way plaintiffs could successfully attribute the condition to use of Meridia. *Meridia*, *supra*, 328 F. Supp. 2d at 799.

The court in *Meridia* held that "epidemiological evidence is just one method of proof" and "such evidence is not mandatory." *Id.* at 800. In fact, "no court has held that epidemiological evidence is necessary to establish general causation when other methods of proof are available." *Id.* at 801.[7] This is so even where the injuries alleged may occur in the absence of the use of the drug or product. *See Ashburn v. Gen. Nutrition Ctrs., Inc.*, 533 F. Supp. 2d 770, 774 (N.D. Ohio 2008);

[7] Although the court in *Meridia* granted, in part, defendants' motion to strike plaintiffs' expert, it did so, as discussed below, because it found he was not qualified to offer his opinions, and his conclusions were not based on a reliable methodology, not because he failed to present epidemiological evidence. 328 F. Supp. 2d at 806.

Rider v. Sandoz Pharm. Corp., 295 F.3d 1194, 1199 (11th Cir. 2002); *Zuchowicz v. United States*, 140 F.3d 381 (2d Cir. 1999).

Again, however, as the court noted in *Meridia*, "[w]hen an expert does not rely on the primary methodology for establishing causation, then that places a burden on the expert to explain his choice of methodologies." *Meridia*, *supra*, 328 F. Supp. 2d 791, 800 (N.D. Ohio 2004) (internal quotations omitted). Blanket exclusion of plaintiffs' experts is therefore inappropriate, and I shall determine whether each expert has met this burden.

2. Plaintiff's Experts

Plaintiffs offer the expert testimony of Drs. Hoppensteadt, Jeske, Kiss, Buncher, Luke and Ohr. Defendants urge the court to exclude all of these experts' opinions, arguing that they are not qualified to offer their opinions, they rely on evidence that is insufficient as a matter of law to establish causation, and their opinions are unreliable.

a. Dr. Debra Hoppensteadt

Dr. Hoppensteadt is a certified medical technologist and licensed clinical pathologist specializing in hematology. She holds bachelor's and master's degrees in medical laboratory science from the University of Illinois. She earned a doctorate of philosophy in vascular surgery from the University of London. She is a professor of pathology and pharmacology at Loyola University of Chicago Stritch School of Medicine and the technical director of the Hemostasis and Thrombosis Research Laboratories at Loyola, where she has worked since 1982. Dr. Hoppensteadt has served on editorial and review boards for numerous scientific publications and seminars and has authored or contributed to more than 490 scientific articles, books and book chapters.

The Loyola laboratory contracts with other research centers and foundations, pharmaceutical companies and federally funded programs. Its activities include the development and validation of methods of investigation into mechanisms involved in the pathogenesis of vascular and thrombotic disorders, and monitoring and studying new antithrombotic and anticoagulant drugs and their effects on the hemostatic and thrombotic processes.

As technical director, Dr. Hoppensteadt is responsible for the overall operation of the laboratories, including monitoring new drugs, consulting with physicians, interpreting test results, and developing and evaluating of drugs and medical devices.

The scientists at the Loyola laboratory, including Dr. Hoppensteadt, are part of a small group of heparin experts who began, following the identification of OSCS as the contaminant in heparin, independently to research and publish articles on the biological effects of contaminated heparin. Dr. Hoppensteadt has authored or contributed to several articles, abstracts, forums and presentations regarding contaminated heparin based on studies or research undertaken by her laboratory.

Dr. Hoppensteadt offers testimony about the chemical structure of heparin, its common uses, the manufacturing process and typical allergic responses or adverse reactions associated with unadulterated heparin. She is prepared to testify about adverse event reports received, preliminary studies to determine the nature of the contaminant, the chemical structure of OSCS, the amount of OSCS found in contaminated heparin and standard procedures that could have prevented the contamination of heparin with OSCS.

It is Dr. Hoppensteadt's opinion that contaminated heparin triggers activation of multiple biological pathways that generate protein mediators, affecting inflammation, coagulation and immunology. This activation, she states, can result in anaphylactoid-type responses such as those

recognized by the CDC case definition. In addition, this activation, in her view, can lead to increased risk of HIT, stronger anticoagulant and bleeding effects, enhanced immunogenic effects of heparin complexes with platelet factor 4, and modification of cell signaling pathways.

She believes that activation of these overlapping biological pathways, particularly in compromised patient populations, can cause immediate or delayed reactions as well as ongoing symptomatology, which can lead to organ failure and death. She also opines that the activation of kallikrein and subsequent formation of bradykinin contributes to the pathogenesis of sepsis.

Her opinions are based on her experience and education, her own research and study of contaminated heparin, the science of immune responses and the published research of others. Her opinion draws on animal studies, *in vitro* studies, clinical reports, case series and adverse event reports.

i. Qualifications

As defendants acknowledge, Dr. Hoppensteadt is "an articulate and qualified pharmacologist." [Doc. 576, at 2]. For twenty-five years she has devoted her research primarily to studying heparin. Since the contaminant in heparin was first identified as OSCS, Dr. Hoppensteadt has conducted numerous studies on the biological effects of OSCS.

I find Dr. Hoppensteadt is unquestionably qualified to testify about the pharmacological and biological effects of contaminated heparin.

Defendants argue, however, that Dr. Hoppensteadt is not qualified to offer opinions as to human causation. Citing *Meridia*, *supra*, 328 F. Supp. 2d at 806, they assert that in the Sixth Circuit, a pharmacologist "is not competent for purposes of general causation."

The district court in *Meridia* considered the admissibility of causation testimony of Dr. Schwartz, a pharmacologist with a doctorate in pharmacy and pharmacology. Contrary to defendants' implied characterization of the opinion, the district court did not find that pharmacologists, as a matter of law, could not offer general causation testimony for any human injury. Rather, the district court found Dr. Schwartz lacked the necessary expertise to testify about the effects of Meridia and some of his conclusions lacked a proper foundation.

In particular, the court noted that "plaintiffs make no showing that Schwartz's expertise in pharmacology provides him with the qualifications to comment on adverse cardiovascular events," that Schwartz lacked expertise on obesity, and that his conclusion that Meridia caused high blood pressure relied on circular logic. *Id.* at 805. Dr. Schwartz's testimony was riddled with assumptions and logical leaps: "Schwartz first starts with the conclusion that Meridia causes high blood pressure then hypothesizes about the mechanisms of how the drug caused that result. Such analysis cannot be used as evidence of causation." *Id.*

The court in *Meridia* conducted a fact-specific inquiry in determining whether Dr. Schwartz possessed the qualifications to offer his opinions, and whether there was a proper foundation for his conclusions. The court in *Meridia* did *not* find that a pharmacologist could not offer general causation testimony, but rather that Dr. Schwartz's testimony as an expert should be limited to the marketing and packaging of Meridia, and that his testimony would not assist the Meridia plaintiffs in creating a genuine issue of material fact with regard to causation. *Id.* at 806–807.

Defendants would have me infer a *per se* rule that a pharmacologist is not competent to testify for the purposes of general causation. But insistence on a certain kind of degree or background is "at odds with the 'liberal thrust' of the Federal Rules and their 'general approach of

relaxing the traditional barriers to "opinion" testimony.'" *Daubert*, *supra*, 509 U.S. at 588. "The language of Rule 702 and the accompanying advisory committee notes make clear that various kinds of 'knowledge, skill, experience, training, or education,' qualify an expert as such." *In re Paoli R.R. Yard PCB Litig.*, 916 F.2d 829, 855 (3d Cir. 1990).

As the court in *Meridia* did with Dr. Schwartz, I must assess whether Dr. Hoppensteadt's knowledge, skill, experience, training and education support her offered opinions on the effects of contaminated heparin in humans.

Defendants are correct that the fact that Dr. Hoppensteadt regularly consults with physicians does not, of itself, give her any clinical expertise. But it is also true that, unlike Dr. Schwartz in *Meridia*, many of Dr. Hoppensteadt's opinions are based on her own research, and her experience and education would enable her to connect this research to well-understood mechanisms and effects in the human body. *Compare Meridia*, *supra*, 328 F. Supp. 2d at 805–806 (excluding pharmacologist testimony where expert relied solely on education, training, and experience, and showed no expertise regarding the alleged injury, adverse cardiovascular events).

Plaintiffs must still show that Dr. Hoppensteadt reliably applied her research, education and experience to the facts in reaching her opinions. Fed. R. Evid. 702 advisory committee note. But where, as here, a pharmacologist possesses the relevant expertise such that she could testify regarding well-known effects in the human body, the question shifts to whether she applied that expertise reliably.

ii. Reliability

(a) Animal and *In Vitro* Studies

Defendants claim that Dr. Hoppensteadt bases her analysis almost entirely on *in vitro* and animal studies. Such studies, according to the defendants, provide, as a matter of law, an insufficient basis for a causation opinion.

As discussed above, *in vitro* and animal studies may be used to show causation. *See*, *e.g.*, *Schott*, *supra*, 696 F. Supp. 2d at 905 (observing that animal and *in vitro* studies are "all recognized and accepted scientific methodologies, used for assessing the possible side-effects and hazards associated with particular drugs and the causes of disease"); *McClellan*, *supra*, 710 F. Supp. 2d at 1113 (noting that case studies, *in vitro* and animal studies "are routinely reviewed and relied upon by physicians in the normal course of their profession, as evidenced by a review of the medical literature").

In vitro and animal studies "can provide a reliable basis for medical and scientific opinions as long as their extrapolations are warranted." *In re Human Tissue Prods. Liab. Litig.*, 582 F. Supp. 2d 644, 663 (D.N.J. 2008); *see General Elec. Co. v. Joiner*, 522 U.S. 136, 144 (1997); *In re Prempro Prods. Liab. Litig.*, 738 F. Supp. 2d 887, 894 (E.D. Ark. 2010); *In re Accutane Prods. Liab.*, 511 F. Supp. 2d 1288, 1291–92 (M.D. Fla. 2007).

Dr. Hoppensteadt's opinions are not based on either animal or *in vitro* studies alone. She relied on both of these types of studies in combination with ecologic studies, review of one of the epidemiological studies on which defendants rely, and reviews of the literature. "Analogy, inference and extrapolation can be sufficiently reliable when the expert's opinion is the kind that a reasonable scientist or physician would make in a decision of importance arising in the exercise of his [or her] profession outside the context of litigation." *Monroe v. Zimmer U.S. Inc.*, 2011 WL 534037, *16

(E.D. Cal. Feb. 14, 2011) (quoting *McClellan*, *supra*, 710 F. Supp. 2d at 1110). Moreover, as in *Monroe* and *McClellan*, this is a case in which it would be unethical to conduct studies on humans.

Dr. Hoppensteadt's opinions cannot be excluded as a matter of law for her reliance on animal and *in vitro* studies, though plaintiffs must demonstrate the reliability of her extrapolations from these studies. *See* Fed. Jud. Ctr., *Reference Manual on Scientific Evidence* at 33 (2d ed. 2000) ("The Court is more interested in focusing on 'how and why' causation could be inferred from the particular evidence being proffered than in formulating per se rules about the admissibility or inadmissibility of categories of evidence to prove causation.").

(b) Adequate Basis: Biological Mechanisms

Defendants allege that Dr. Hoppensteadt's opinions are flawed because the *in vitro* studies she cites "come to conflicting conclusions about the biological effects she hypothesizes." [Doc. 528-1, at 47]. In particular, defendants state that Dr. Hoppensteadt admits that contaminated heparin does not increase plasmin or thrombin-like activity compared to heparin and that there are studies that have obtained different results with respect to whether OSCS can trigger increased thrombin. Defendants point out that heparin itself limits thrombin formation. They also state that there are conflicting studies on whether OSCS activates the complement system. Finally, they state that "studies have shown that contaminated heparin is *not* associated with an increase in functional antibodies." [Doc. 528-1, at 48] (citing Cafer Adiguzel, *et al.*, *Increased Prevalence of Antiheparin Platelet Factor 4 Antibodies in Patients May Be Due to Contaminated Heparin*, 15 Clin. App. Thromb. Hemost. 145, 148 (2009)) (emphasis in original).

In the *Daubert* hearings, Dr. Hoppensteadt testified that while the contaminated heparin had antithrombotic and anticoagulant effects, the OSCS also causes inflammation and activation of the

contact system. Dr. Hoppensteadt explained, "when we talk about hemostasis, we have to talk about a check and balance. So depending on the patient's predisposing factors and depending on the OSCS, the OSCS could set that balance into thrombotic balance as opposed to the antithrombotic." [Doc. 573, at 109].

She also explained that, although the contaminant did not change the anticoagulant potency as measured by the U.S.P. type assay, this assay is "not a very specific type test." *Id.* Dr. Hoppensteadt testified in deposition that studies have obtained different results with respect to whether OSCS can trigger increased thrombin, and, in her opinion, these differences resulted from differing dosages of heparin and the sensitivity of the assays performed. [Doc. 528-4, at 19].

Defendants are correct that the Adiguzel study, of which Dr. Hoppensteadt was a co-author, found no statistically significant difference in terms of the prevalence of AHPF4 antibodies as measured by the ^{14}C-Serotonin Release Assay (^{14}CSRA) between normal plasma, plasma obtained from 2006-2007 (exposed to noncontaminated heparin), and plasma obtained in 2008 (exposed to contaminated heparin).[8]

The Adiguzel study found a statistically significant difference in AHPF4 antibodies between the groups as measured by "a sandwich-type immunoassay," GTI ELISA.[9] The study's authors also noted a "faster and stronger platelet aggregation in the presence of AHPF4 antibodies" in the presence of contaminated heparin as opposed to uncontaminated heparin.[10] The study's authors

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[8] Cafer Adiguzel, *et al.*, *Increased Prevalence of Antiheparin Platelet Factor 4 Antibodies in Patients May be Due to Contaminated Heparin*, 15(2) Clinical & Applied Thrombosis/Hemostasis 145, 147 (2009).

[9] *Id.*

[10] *Id.* at 148.

opined that the [14]CSRA responses suggest that OSCS may be responsible for an increased generation of antibodies having a lower platelet aggregation potential, which accounted for the lack of thrombocytopenic response in the study.[11] They concluded that the presence of OSCS in heparin may enhance immunogenic effects of heparin complexes with PF4, and stated that the clinical implications warrant further studies relative to the long-term effects of these antibodies, which also bind to heparin alone and may modulate the therapeutic actions of heparins.[12] The Adiguzel study was subjected to peer review and publication.

Dr. Hoppensteadt's testimony demonstrates that she has not ignored or overlooked the evidence to which defendants point. She explains her rationale for nevertheless reaching the conclusions she reaches about the biological mechanisms at work in these studies. The Supreme Court in *Daubert* "intended to exclude 'junk science'—unsupported testimony or evidence cloaked in the credentials of a testifying expert—that would confuse or mislead rather than 'assist the trier of fact.'" *McClellan, supra*, 710 F. Supp. 2d 1101 (quoting *Best v. Lowe's Home Ctrs., Inc.*, 563 F.3d 171, 176–77 (6th Cir. 2009)). The fact that different studies have obtained different results does not render Dr. Hoppensteadt's opinions "junk science."

"There are no certainties in science," *Daubert*, 509 U.S. at 590, and establishing reliability does not mean that plaintiffs must prove that the assessments of their experts are correct. *McClellan, supra*, 710 F. Supp. 2d at 1101–102, 1106. Perceived weaknesses in the conclusions, such as those identified here by defendants, go to weight rather than to admissibility. *See McClellan, supra*, 710 F. Supp. 2d at 1106 ("Importantly, it is not the court's role to decide whether the proffered testimony

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[11] *Id.*

[12] *Id.* at 150.

sufficiently proves [causation]; rather, it is the court's duty to ensure that the proffered testimony is sufficiently reliable to be admitted at trial for consideration by the trier of fact.").

(c) Adequate Basis: Effects in Humans

Defendants assert that Dr. Hoppensteadt's opinions are completely unsupported as to the resulting human effects of these biological mechanisms. Defendants argue that Dr. Hoppensteadt has no scientific basis for her opinions that either: 1) increased kallikrein activity or feedback loops occur in humans; or 2) such increased kallikrein activity in turn causes adverse clinical effects.

(I) Occurrence in Humans

Defendants recite that there are no studies either looking at the effects of OSCS in causing feedback loops or measuring any compliment system activation in human beings administered OSCS. They also point to Dr. Hoppensteadt's acknowledgment that "there's substances in human beings that prevent kallikrein from leading to clinical symptoms." Based on these facts, defendants assert that it is "well-settled science . . . that the mechanism upon which plaintiffs rely is *not* plausible in humans or animals." [Doc. 576, at 5] (emphasis in original).

Dr. Hoppensteadt explained that she relied on published studies and her own research in forming her opinion that increased kallikrein activity and feedback loops occur in human beings. The Kishimoto study showed that OSCS caused contact and complement activation.[13] Specifically, the Kishimoto study found that OSCS directly activated the kinin-kallikrein pathway in human plasma, leading to the generation of bradykinin, and that OSCS also generated the anaphylatoxins

[13] Takashi Kei Kishimoto, *et al.*, *Contaminated Heparin Associated with Adverse Clinical Events and Activation of the Contact System*, 358 New Eng. J Med. 2457, 2457 (2008).

C3a and C5a.[14] In the study, OSCS contaminated heparin and synthetically-derived OSCS both induced hypotension when administered by infusion in swine.[15]

Plaintiffs contend several studies support Dr. Hoppensteadt's conclusion about the occurrence of the biological mechanism in humans. Some of the studies accepting that these mechanisms are at work in human beings exposed to OSCS contaminated heparin are the same defendants on which seek to rely to block plaintiffs' claims. The Blossom study "found similar biologic activity among multiple vials of heparin that were known to result in adverse reactions, and the clinical picture described among the outbreak cases nationally is consistent with the biologic mediators previously identified in response to OSCS."[16]

The McMahon study, another epidemiologic study of contaminated heparin, also concluded that "the mechanism of OSCS kallikrein activation fits the observed events and thus provides biological plausibility to OSCS mediated AEs."[17]

In addition to these studies, Dr. Hoppensteadt's opinions rest on her research, involving both *in vitro* and animal studies. Dr. Hoppensteadt and other researchers have relied for the most part on animal and *in vitro* tests in researching the effects of OSCS contaminated heparin for two reasons. First, as already noted, it would be unethical to test OSCS in human beings. Second, identifying the appropriate patient groups to conduct epidemiological studies would be both difficult and expensive.

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[14] *Id.*

[15] *Id.*

[16] Blossom, *supra* note 1, at 2680–81.

[17] McMahon, *supra* note 2, at 928.

Nonetheless, plaintiffs retain the burden of demonstrating that Dr. Hoppensteadt has appropriately extrapolated from these studies.

Dr. Hoppensteadt explained that "pigs are similar to similar to humans . . . [T]his pig model . . . is an established model that's used for cardiopulmonary bypass surgery because it's a large animal and because the amount of blood that is needed to be drawn to do these analysis." [Doc. 573, at 152].[18] Use of pigs is further supported by the Kishimoto study.[19] As part of this study, researchers screened plasma samples from various species.[20] These samples indicated that swine and humans are sensitive to the effects of OSCS in a similar manner.[21]

As the Federal Judicial Center's Reference Manual on Scientific Evidence, at 410, notes, "[i]n qualitative extrapolation, one can usually rely on the fact that a compound causing an effect in one mammalian species will cause it in another species."

Dr. Hoppensteadt testified that the *in vitro* studies would see a different degree of activation than would be present in the human body. [Doc. 573, at 156]. It is her opinion that, depending on the individual patient, the degree of activation in the human body would be greater than that seen in the test-tube due to the presence of white blood cells, red blood cells and endothelial cells. *Id.* She explained that her extrapolations from the *in vitro* studies are "based on what we know about the well-established feedback loop systems." [Doc. 573, at 150].

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[18] Dr. Hoppensteadt also explained that ethical considerations also prevented injecting OSCS into monkeys, which have a very similar coagulation system to humans. [Doc. 573, at 152].

[19] Takashi Kei Kishimoto, *et al.*, *Contaminated Heparin Associated with Adverse Clinical Events and Activation of the Contact System*, 358 New Eng. J Med. 2457, 2457 (2008).

[20] *Id.*

[21] *Id.*

Dr. Hoppensteadt has followed reliable methodology in reaching her opinions that contaminated heparin can cause contact and complement activation in human beings.

(ii) Adverse Effects in Humans

Defendants argue that even if Dr. Hoppensteadt can opine that contaminated heparin activates such pathways in humans, she cannot give a reliable scientific opinion as to any adverse effects caused by such activation. Defendants therefore seek exclusion of Dr. Hoppensteadt's testimony as to general causation of bleeding, clotting, HIT, sepsis and symptoms occurring after sixty minutes, arguing that such testimony is speculative. Defendants also seek exclusion of Dr. Hoppensteadt's testimony regarding dosing, specifically that any concentration of contamination in heparin can cause harm and that subcutaneous administration can result in harm.

As discussed above, plaintiffs must demonstrate that Dr. Hoppensteadt based her opinions about adverse effects in human beings on reliable science. First, as a pharmacological researcher rather than a physician, she must be able to explain how she reached her opinions on effect. Second, where her opinions on adverse effects in humans derives from animal and *in vitro* studies, she must explain why extrapolation to human beings is appropriate.

(aa) Bleeding

Dr. Hoppensteadt's proffered opinions on the bleeding effects of contaminated heparin are based on reliable methodology. She derives her opinion, in part, on a publication based on *in vitro* and *in vivo* (rat) studies performed in her laboratory.[22] The *in vitro* studies showed that OSCS exhibited measurable anti-coagulant activity and produced supra-additive effects in the presence of

[22] Jawed Fareed, *et al.*, *Biological Profile of the Hyper/Oversulfated Chondroitin Sulfate Contaminant Isolated from Recalled Heparin,* 34:1S Seminars in Thrombosis & Hemostasis 119, 119 (2008).

heparin.[23] In the animal models of thrombosis and bleeding, the contaminated heparin produced stronger anti-coagulant effects than heparin.[24]

Dr. Hoppensteadt testified that the biological mechanisms predicted such a response, explaining that "[i]f you have activation of coagulation system in the feedbacks that are occurring and you have a decrease in the fibrinolytic inhibitors, based on the specific disease of the patient, you can end up with a propensity of the patient to bleed." [Doc. 573, at 66]. In doing so, she identifies the particular patient-specific factor, decrease in fibrinolytic inhibitors, that would interact with the biological mechanism identified to cause the result in the patient.

Other studies also acknowledge the existence and probable mechanism of bleeding effects associated with contaminated heparin.[25] Dr. Hoppensteadt indicated that there is no dispute in the scientific community that OSCS contaminated heparin can cause an increased risk of bleeding complications. [Doc. 573, at 66].

Dr. Hoppensteadt acknowledged that bleeding is a known risk of heparin, even apart from contamination. She also acknowledged that she had not reviewed any specific cases of patient bleeding. Her opinion is nevertheless sufficiently reliable to be admissible under Rule 702. *See In re Paoli, supra,* 35 F.3d at 744 ("[Plaintiffs] do not have to demonstrate to the judge by a preponderance of the evidence that the assessments of their experts are *correct*, they only have to demonstrate by a preponderance of the evidence that their opinions are reliable.").

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[23] *Id.*

[24] *Id.*

[25] Boyangzi Li, *et al.*, *Oversulfated Chondroitin Sulfate Interaction with Heparin-Binding Proteins: New Insights into Adverse Reactions from Contaminated Heparins*, 78 Biochemical Pharmacology 292 (2009). ("OSCS can also affect the fibrinolytic system, activating plasminogen, possibly explaining the bleeding effects associated with OSCS contaminated heparin.").

(bb) Clotting

Defendants seek to exclude testimony by Dr. Hoppensteadt regarding clotting effects caused by contaminated heparin. The defendants appear to refer to clotting effects distinguishable from HIT—that is, clotting resulting from any reduced efficacy of contaminated heparin as opposed to clotting induced by contaminated heparin. Dr. Hoppensteadt's expert report does not discuss this effect, and plaintiffs do not make any showing that any such opinion offered by Dr. Hoppensteadt is based on reliable methodology. Dr. Hoppensteadt may not testify as to such clotting effects.

(cc) HIT

It is Dr. Hoppensteadt's opinion that OSCS contaminated heparin causes an increased risk of HIT. Dr. Hoppensteadt explained that this opinion is based on the Adiguzel study conducted at Loyola, which she co-authored, and a review of relevant scientific literature on contaminated heparin and HIT.

The Adiguzel study looked at blood samples of patients undergoing hemodialysis. The study found that the group treated during the contamination period experienced a substantial increase in the incidence of the heparin platelet factor 4 antibody. Dr. Hoppensteadt testified that none of the patients in the study actually experienced the drop in platelet count signifying the development of HIT. She and her co-authors believe, however, that the increase in these antibodies may increase the risk of these patients to develop HIT.

Dr. Hoppensteadt supports this opinion with two articles by Drs. Greinacher and Warkentin. Drs. Greinacher and Warkentin are well-respected in the field of HIT. Dr. Hoppensteadt testified that their textbook, *Heparin-Induced Thrombocytopenia*, "is considered the Bible when it comes to heparin induced thrombocytopenia." [Doc. 573, at 70].

In a letter to the editor responding to the Kishimoto study, Drs. Greinacher and Warkentin discussed the likelihood that OSCS, a hyper-sulfated polysaccharide, could induce HIT. They stated that during the period of contamination, they observed a substantial increase in laboratory-confirmed heparin-induced thrombocytopenia in Germany, but not in Canada. They suggested that this association may reflect differences in distribution of OSCS-contaminated heparin, as Canada saw only a minimal recall of products and no reports of anaphylactic reactions.

Drs. Greinacher and Warkentin followed this letter to the editor with an article arguing that OSCS-contaminated heparin could increase the risk of HIT. They wrote that the discovery of OSCS in heparin "recalled an intriguing finding in the early history of HIT in which a hypersulfated chondroitin sulfate (essentially identical to OSCS) formerly used to treat degenerative arthritis, was also identified to cause a disorder identical to HIT."[26] They explained that "[t]he very high DS [degree of sulfation] of OSCS (4.0) contaminating UFH [unfractionated heparin] is a key feature supporting a higher immunization rate compared with non-contaminated UFH."[27]

Dr. Hoppensteadt explained that the article was referring to a case study on Arteparon, which reported that a patient receiving the hypersulfated chondroitin sulfate was more prone to thrombosis because of the positive charge of the platelet factor 4 and the negative charge of the hypersulfated chondroitin sulfate. [Doc. 573, at 72].

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[26] Warkentin, *et al.*, *Heparin-induced anaphylactic and anaphylactoid reactions: two distinct but overlapping syndromes*, Expert Opinion on Drug Safety 8, no. 2: 129–144 (March 2009).

[27] *Id.*

Dr. Hoppensteadt also discussed more recent studies examining OSCS's ability to induce thrombin generation, and noted that a paper authored by Qian, *et al.*[28] also concluded that the effects seen in their studies suggest a higher incidence of HIT among patients receiving contaminated heparin. [Doc. 573, at 72]. Dr. Hoppensteadt also testified that there is no dispute in the scientific literature that OSCS can cause an increased risk of HIT. *Id.*

Dr. Hoppensteadt's opinion that OSCS contaminated heparin increases the risk of HIT is supported by her research and the published studies of others. Looking at any one of these studies, alone and without cognizance of the others, a judge would be unable to identify a reliable basis for concluding that contaminated heparin increases the risk of HIT. But looking at them together, the picture is very different.

Courts have admitted expert testimony as reliable where experts extrapolate their opinions from their knowledge and experience combined with a review of the relevant scientific literature. *See*, *e.g.*, *McClellan*, *supra*, 710 F. Supp. 2d at 1131. Dr. Hoppensteadt has done so here, and I find that her opinions as to HIT are sufficiently reliable. This evidence may not provide as conclusive a foundation as an epidemiological study, but that fact goes to weight, rather than admissibility.

(dd) Sepsis

Dr. Hoppensteadt opines that contaminated heparin can cause a sepsis-like response or aggravate sepsis or disseminated intravascular coagulation (DIC). There has been no study that has looked at OSCS contaminated heparin and its effects in septic patients.

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[28] Yi Qian, *et al.*, *Oversulfated Heparin By-products Induce Thrombin Generation in Human Plasma Through Contact System Activation*, 16(3) Clinical & Applied Thrombosis/Hemostasis 244 (2010); Yi Qian, *et al.*, *Heparin and Oversulfated Heparin Byproduct Induce Thrombin Generation Through Contact System Activation in Plasma of Patients with HIT*, 16(3) Clinical & Applied Thrombosis/Hemostasis 251 (2010).

Dr. Hoppensteadt bases her opinion on literature regarding "feedback loops" and the fact that OSCS contaminated heparin activates the complement system. Dr. Hoppensteadt explained that "complement activates inflammation. Inflammation then is able to, through the feedback loops, activate coagulation. And then we get this almost like a snowball effect." [Doc. 573, at 64]. She explained that because of all the activation, the symptoms can present like a patient who has an infection—"the patient's response in the coagulation in the blood is very similar to what we see in patients with an infection." [Doc. 573, 64].

Dr. Hoppensteadt presents nothing that would link the feedback loop responses she theorizes based on the literature to patients exposed to contaminated heparin. She has done no experiments demonstrating the ability of OSCS or OSCS contaminated heparin to cause such feedback loops, nor can she point to studies published by others. She has shown that OSCS contaminated heparin can activate the complement system, but she has not shown by any methodology that this initial activation leads to the inflammation and coagulation responses she theorizes. Moreover, she testifies that a sepsis-like response will depend on the specific co-morbidities of the patient, without detailing what diseases or co-morbidities may make such a response more or less likely.

With regard to this aspect of her testimony, there is "simply too great an analytical gap between the data and the opinion proffered." *Gen. Elec. Co. v. Joiner*, 522 U.S. 136, 146 (1997). Untested hypotheses, even if plausible, are insufficient to satisfy Rule 702. *Rider v. Sandoz Pharm. Corp.*, 295 F.3d 1194, 1202 (11th Cir. 2002) ("The courtroom is not the place for scientific guesswork, even of the inspired sort."); *see Tamraz v. Lincoln Elec. Co.*, 620 F.3d 665, 670 (6th Cir. 2010) (explaining that a "working hypothesis" is not "admissible scientific knowledge").

(ee) Symptoms Occurring After Sixty Minutes

Dr. Hoppensteadt stated in her expert report and at the *Daubert* hearing that her research found increased kallikrein activity beyond the sixty-minute time-frame examined by Kishimoto, *et al.* She explained that the Kishimoto study reported results showing increased kallikrein activity at the end of the sixty-minute observation time. From these studies, Dr. Hoppensteadt opines that contaminated heparin could cause effects beyond the sixty-minute time period—well beyond the time-frame established by the CDC case definition for onset of symptoms.

Dr. Hoppensteadt points to no observable effects experienced by the animals in these studies beyond a few minutes after administration. She theorizes that the kallikrein activity could activate feedback loops, but she does not explain the process by which the onset of symptoms would be delayed, or initiated after sixty-minutes, except to say that it may depend on patient-specific factors she does not define.

Dr. Hoppensteadt has shown that there is increased kallikrein activity, but her opinion that this activity can have effects beyond the sixty-minute time period is speculative.

(ff) Percent Contamination

Dr. Hoppensteadt testified during the hearing that "there's not a dose response. It doesn't matter if we have the higher dosages—or the percentages of OSCS can cause as much activation as the lower concentrations." [Doc. 573, at 73]. She stated that "there is no acceptable level of OSCS." *Id.*

Dr. Hoppensteadt briefly explained at the hearing that her opinion that there is not a dose response is "based on the additional work of Blossom and some of our studies." *Id.* Her expert report does not discuss the concentration of OSCS contamination. Plaintiffs' brief provided details of some of these studies, showing, for example, that the Kishimoto *et al.* observed that "contaminated

heparin showed a bell-shaped dose response, which is typical of glycosaminoglycan-mediated responses."[29] Many of the lots tested in the Kishimoto study had OSCS concentrations less than fifteen percent, and some of these lots showed more kallikrein activation than the highest concentrations of OSCS.

This evidence supports Dr. Hoppensteadt's retraction of her earlier letter to the editor expressing the opinion that "it is likely that some heparin products with smaller amounts of (<15%) OSCS may . . . have been used without any sizeable adverse effects." But it does not indicate that there is *no* dose response. Plaintiffs have not carried their burden of demonstrating that Dr. Hoppensteadt has a reliable foundation for the opinion that there is no dose response.

Dr. Hoppensteadt's opinion that there is no acceptable level of OSCS is common-sense. OSCS is a contaminant of heparin lacking FDA approval and has not been shown to be safe at any threshold. Testimony by an expert that there is no acceptable level of OSCS has the potential to mislead the jury. Such testimony may be misinterpreted as confirming the harmfulness of OSCS in even the slightest concentrations. Before the FDA, it is the pharmaceutical company's burden to show that a product is safe. But before a court of law, it is the plaintiff's burden to show a product caused injury. I believe, however, that a jury is capable of understanding this distinction. Cross-examination and instruction will dispel any possible confusion on this point.

(gg) Subcutaneous Administration

Dr. Hoppensteadt opines that OSCS is capable of being absorbed after subcutaneous administration and therefore can cause harm in patients. [Doc. 33-7, at 21]. She bases this opinion on an abstract she co-authored describing a study undertaken to determine the pharmacokinetic

[29] Kishimoto, *et al.*, *supra,* at 2461.

profile of OSCS in rats after intravenous and subcutaneous administration.[30] Blood samples taken from the rats demonstrated that OSCS was absorbed after subcutaneous administration. Dr. Hoppensteadt does not explain, nor does the abstract elucidate, how human effects could be extrapolated from these results in rats. Nor does she explain how she arrived at her opinion that the study confirms that subcutaneous administration of contaminated heparin can cause harm in patients (a conclusion not part of the published abstract). Again, I find there is "simply too great an analytical gap between the data and the opinion proffered." *Joiner*, *supra*, 522 U.S. at 146.

iii. Relevance

Where reliable, the opinions advanced by Dr. Hoppensteadt "logically advance[] material aspect[s] of the proposing party's case." *Daubert*, *supra*, 43 F.3d at 1315. Dr. Hoppensteadt's explanations of the biological mechanisms and different laboratory tests are also helpful to the jury in weighing the evidence and understanding the basics of the science. I do not doubt that some of her testimony may confuse the jurors—such is the nature of complex scientific evidence. But it is not misleading, and her testimony and opinions will no doubt be clarified through the skill of the parties' attorneys and by proper instruction on the burden of proof.

b. Dr. Walter Jeske

Dr. Jeske is the director of platelet research at the Hemostasis Research Laboratories of the Loyola University Medical Center. He also serves as a clinical instructor in medical technology at the School of Related Health Sciences of the Rosalind Franklin University. He has previously

[30] Angel Losadal, *et al.*, *Bioavailability of oversulfated chondroitin sulfate in rat: Pharmacological implications in contaminated heparins*, available online at http://www.fasebj.org/cgi/content/meeting_abstract/23/1_MeetingAbstracts/LB401.

worked as an assistant professor at the Loyola University Medical Center in the thoracic cardiovascular surgery and pathology departments.

Dr. Jeske holds a bachelor's degree in biochemistry from Illinois Benedictine College and a doctorate of philosophy in pharmacology from Loyola University. His dissertation addressed the comparative pharmacology of synthetic heparin analogs having specific interaction with either antithrombin or heparin cofactor II.

Since completing his doctoral studies, Dr. Jeske has focused on platelet analysis techniques and their application to the study of heparin-induced thrombocytopenia. He has conducted research on behalf of federally funded programs, pharmaceutical companies, and other research foundations, many involving the study of heparin and its biological effects. Dr. Jeske has taken part in studies designed to examine the impact of heparin contaminant on the hemostatic effects of unfractionated and low molecular weight heparins. He was part of a group that isolated and characterized the contaminant in heparin.

Dr. Jeske is a peer-reviewer for eleven scientific and medical journals and the International Society of Thrombosis and Hemostasis. He has authored or contributed to well over 450 scientific articles, abstracts, books, book chapters, and presentations, a great number of which relate to the study of heparin and six of which relate to studies involving contaminated heparin.

Several of Dr. Jeske's opinions in this case relate to testing and the source of contamination. These opinions are addressed in other motions by defendants, and as they do not pertain to the question of general causation, I do not address them here.

Relating to general causation, Dr. Jeske opines that OSCS-contaminated heparin activates both the contact and complement systems, and is a potent bradykinin generator. It is Dr. Jeske's

opinion that OSCS-contaminated heparin induces thrombin-like activity and exposure results in the generation of complement anaphylatoxin C5a, which, more likely than not, caused the hypercoagulability observed in patients with chronic renal failure who are maintained on hemodialysis. He also opines that OSCS-contaminated heparin substantially increases the risk of HIT, and contributes to the risk of adverse outcomes in hemodialysis patients.

i. Qualifications

As discussed above, there is no *per se* rule that a pharmacologist may not testify as to general causation.

Dr. Jeske acknowledged that he had only a "layperson's understanding" of anaphylactoid reactions, but he does not offer any opinions regarding anaphylactoid reactions.

Dr. Jeske is a qualified researcher with significant experience with heparin and contaminated heparin. His opinions must be reliably based on his experience and expertise, and if they overreach that expertise, they will be excluded.

ii. Reliability

Defendants charge that Dr. Jeske's opinions are unsupported and unreliable. They argue that the evidence regarding the complement system and thrombin generation is conflicting. They also argue that there is a lack of data demonstrating these biological pathways occur in humans, or that they cause any adverse health effects.

(a) Conflicting Evidence

Defendants' complaints about conflicting evidence are unavailing. In their brief, they state that Dr. Jeske "acknowledged that there are studies that 'did not demonstrate an increase in

complement activation upon incubation of plasma with OSCS.'" [Doc. 528-1, at 54]. The sense of this acknowledgment is better understood when quoted in full:

> In contrast to the report from Kishimoto, this study did not demonstrate an increase in complement activation upon incubation of the plasma with OSCS. This may be related to the use of heparin to anticoagulate blood samples in this study and heparin's ability to inhibit kallikrein and factor XIIa activity.

Jeske Rpt. at 23.

Dr. Jeske acknowledges that the study came to a different result, but he criticizes the methods of the study. The study in question is the McKee study,[31] financed by Baxter.

Dr. Jeske does not ignore the conflicting results, but he explains why he relies on the results of the Kishimoto and Adam study[32] rather than those reached by McKee *et al.*

The evidence on these issues is not wholly consistent, and experts could reach different conclusions. The Court recognized in *Daubert* that there is a range in which experts might reasonably differ on issues of science, and that such conflicting evidence should be admitted to aid the jury in deciding those issues. *Kumho*, 526 U.S. at 153. The Sixth Circuit elaborated:

> 'Scientific knowledge' establishes the standard of evidentiary reliability, and to be considered appropriately scientific, the expert need not testify to what is 'known' to a certainty but must only state an inference or assertion derived by the scientific method. Testimony meets this threshold when an expert, whether basing testimony on professional studies or personal experience, employs in the courtroom the same level of intellectual rigor that characterizes the practice in the relevant field.

Jahn v. Equine Serv., PSC, 233 F.3d 382, 388 (6th Cir. 2000) (internal citations omitted); *see also U.S. v. Bonds*, 12 F.3d 540 (6th Cir. 1994) ("Absolute certainty of result or unanimity of scientific

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[31] Jeff McKee, *et al.*, *Structure Elucidation and Biological Activity of the Oversulfated Chondroitin Sulfate Contaminant in Baxter Heparin*, 20 J. of Clinical Pharmacology 1159 (2010).

[32] Albert Adam, *et al.*, *Bradykinin Forming Capacity of Oversulfated Chondroitin Sulfate Contaminated Heparin In Vitro*, 22 Biomaterials 5741 (2010).

opinion is not required for admissibility so long as the conclusions drawn by the experts are based on generally accepted and reliable scientific principles.").

I find Dr. Jeske's opinions on the basis of this evidence to be within the range in which experts may reasonably differ.

(b) Biological Pathways in Humans

Defendants state that Dr. Jeske acknowledges that there is a lack of data showing that the biological pathways occur in humans, but what Dr. Jeske actually acknowledged was that he is unaware of any study finding "complement system activation from contaminated heparin in human beings *in vivo*." Jeske Dep. at 72–73. As noted, conducting such a study in humans would be unethical.

Dr. Jeske lists several studies which, together with his experience and expertise, form the basis of his opinion that contaminated heparin can activate the complement system in human beings. A review of his deposition demonstrates his thorough understanding of the science and his professionalism in carefully explaining his answers.

Though there is some disagreement in the scientific literature as to whether contaminated heparin activates the complement system, nonetheless, "[i]n keeping with the court's proper role and the 'liberal thrust' of Rule 702, I will not exclude plaintiffs' expert testimony simply because the evidence supporting it does not establish causation to a scientific or medical certainty." *McClellan*, *supra*, 710 F. Supp. 2d at 1106.

(c) Adverse Effects

Dr. Jeske gives opinions about three adverse effects caused by contaminated heparin: increased risk of HIT; increased risk of adverse outcomes in hemodialysis patients; and hypercoagulability in patients with chronic renal failure who are maintained on dialysis.

(i) HIT

Dr. Jeske's opinion about the increased risk of HIT draws from the same evidence on which Dr. Hoppensteadt's opinion relied—the Greinacher letter to the editor and the Adiguzel study. The Greinacher letter, discussed above, included an ecological study that demonstrated an increased incidence of HIT in a lab in Germany over the contamination period, but no increased incidence in a lab in Canada. Germany saw distribution of contaminated heparin, whereas in Canada, patients saw minimal exposure to any potentially contaminated heparin products.

It is true, as defendants repeatedly point out, that this ecological study does not demonstrate causation. At best, it suggests an association between contamination and HIT. In deposition, Dr. Jeske further elaborated that there may be different patient populations referred to the Canadian and German laboratories, and that he suspected, based on his knowledge of the letter's authors, that they used different functional assays to measure the antibodies. Dr. Jeske nevertheless views the data in the letter to be "a good signal, though, that something's going on with the treatment with contaminated heparin preparations." Jeske Dep. at 134–35 [Doc. 484-1, at 134–35].

The Adiguzel study, discussed in detail above, found an increase in antibodies among patients exposed to contaminated heparin, which "is the signal of increased immunogenicity of the heparin products that were administered during the contamination period." Jeske Dep. at 149. [Doc. 484-1, at 149]. None of the patients in the study developed HIT.

Dr. Jeske explained in deposition that the presence of the antibody "at least put . . . these patients at risk of developing HIT." Jeske Dep. at 150. He also explained that "different patient populations tend to have different incidences of HIT. Those patients that are exposed to more trauma, cardiovascular surgery, orthopedic surgery, tend to have higher levels of HIT than other patients that are—are considered to be more medically managed." The patients in the Adiguzel study were end-stage renal patients on dialysis. Dr. Jeske stated that "the expected incidence of HIT in the dialysis population is relatively small. I think textbooks probably give you 2 to 3 percent incidence. In this case, with only 78 patients in the study, it seemed to be unlikely that you'd—you'd see patients—see a patient that has true clinical HIT." *Id.*

Dr. Jeske opines on the basis of these two sources that contaminated heparin causes an increased risk of HIT. Neither of these sources, taken alone, would reliably demonstrate that it is more likely than not that contaminated heparin substantially increases the likelihood of HIT. But again, taken together with Dr. Jeske's knowledge and experience, these studies are the type of information on which pharmacologists typically rely.

Defendants urge that I exclude Dr. Jeske's opinion because he "concedes that the available data do not establish a link between contaminated heparin and clinical HIT." Dr. Jeske did not make such a concession. He acknowledged, rather, that none of the patients in the Adiguzel study developed a thrombocytopenia problem and that the Greinacher letter did not document any patient as having received contaminated heparin. And I will not exclude expert testimony on the basis that the evidence supporting it does not establish causation to a scientific certainty. *See Daubert*, 509 U.S. at 588.

(ii) Adverse Outcomes in Hemodialysis Patients

Dr. Jeske opines that because contaminated heparin causes an increase of HIT antibodies, it is associated with an increased risk of adverse outcomes in hemodialysis patients, even in the absence of thrombocytopenia or other overt symptoms of HIT. He basis this opinion on the fact that the Adiguzel study demonstrated an increase in anti-heparin/PF4 antibodies, and on two studies which suggested a correlation between the presence of HIT antibodies and an increased risk of adverse outcomes in hemodialysis patients.[33]

As his deposition testimony clarified, the Carrier report on which Dr. Jeske relied was not suited to suggest causality. The authors indicated that their results showed a trend toward increased major cardiovascular events in patients with platelet factor 4 antibodies, but were not willing to make a causal association between antibodies and mortality.

Dr. Jeske stated, "At this point, the data doesn't—isn't strong enough to support, one way or the other, whether [PF4 antibodies] [i]s the marker of some other process or the antibody actually has any effect on its own." Jeske Dep. at 187 [Doc. 484-1, at 187].

Given these admissions, I find there is simply too great an analytical gap between the scientific evidence available and Dr. Jeske's proffered opinion that contaminated heparin contributes to the risk of adverse outcomes in hemodialysis patients.

(iii) Hypercoagulability

Dr. Jeske's proffered testimony includes his opinion that "OSCS contaminated heparin results in the generation of complement anaphylatoxin C5a, which, more likely than not, caused the

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[33] Pena de la Vega, *et al.*, *Association of heparin-dependant antibodies and adverse outcomes in hemodialysis patients: a population-based study*. 80 Mayo Clinic Proceedings 995 (2005); Carrier, *et al.*, *Increased mortality in hemodialysis patients having specific antibodies to the platelet factor 4-heparin complex*, 73 Kidney International 213 (2008).

hypercoagulability observed in patients with chronic renal failure who are maintained on hemodialysis." Jeske Rpt. at 25.

Dr. Jeske explains that the Kishimoto study showed an increase in C5a levels in human plasma supplemented with contaminated heparin, purified contaminant, synthetic OSCS and heparin mixed with synthetic OSCS, supporting his opinion that OSCS-contaminated heparin causes an increase in complement anaphylatoxin C5a levels.

Dr. Jeske also discusses a recently published study examining the mechanisms of thrombosis during hemodialysis.[34] This study demonstrated that complement activation triggered by hemodialysis biomaterials and the subsequent generation of the complement anaphylatoxin C5a results in the expression of functionally active tissue factor in peripheral blood neutrophils. The authors also found that inhibition of complement activation attenuated tissue factor expression in blood passing through a hemodialysis circuit, suggesting that activation of complement may be a cause of hypercoagulability observed in patients with chronic renal failure undergoing dialysis.

Both of the studies on which Dr. Jeske relies are peer-reviewed, published reports, and Dr. Jeske explains how he reaches his conclusion based on the cumulative findings of these reports. Both have been cited by other published articles. I find Dr. Jeske's opinion regarding hypercoagulability to be reliable.

iii. Relevance

Dr. Jeske opines on several matters of general causation, and his testimony is undeniably relevant to that end. Nevertheless, defendants complain that "[m]ost of Dr. Jeske's opinions

[34] Kourtzelis, *et al.*, *Complement Anaphylatoxin C5a Contributes to Hemodialysis-Associated Thrombosis*, 116 Blood 631 (2010).

regarding the biological effects of contaminated heparin consist of a lengthy background dissertation on the biological effects of heparin that, by his own admission, he copied nearly '*verbatim*' from his 1996 Ph.D. thesis." [Doc. 528-1, at 53]. Defendants point out that his thesis does not involve human studies or OSCS contaminated heparin, but rather provides a pharmacological discussion of heparin and other molecules.[35] They therefore conclude that this material is "completely divorced from anything at issue in this case."

Dr. Jeske's opinions do contain a large amount of background information about the biological effects of heparin. Although this background information is not contested in this case, such information is a necessary predicate to an understanding of the contested issues. As the Committee Note to Rule 702 recognizes,

> [I]t might also be important in some cases for an expert to educate the factfinder about general principles, without ever attempting to apply these principles to the specific facts of the case. For example, experts might instruct the factfinder on the principles of thermodynamics, or bloodclotting, or on how financial markets respond to corporate reports, without ever knowing about or trying to tie their testimony into the facts of the case. The amendment does not alter the venerable practice of using expert testimony to educate the factfinder on general principles.

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[35] Defendants also complain that "Dr. Jeske wrote his thesis *before* he received his Ph.D, while he was still a 27- or 28-year-old pharmacology student."[Doc. 528-1, at 54] (emphasis in original). Defendants apparently believe that these facts undermine the reliability of Dr. Jeske's report.

Defendants recite the obvious. As a requirement to *receive* a doctorate degree, any doctoral candidate must write a thesis *before* it can be received. As Dr. Jeske received his Ph.D, presumably on the strength of his thesis, which was peer-reviewed and published, nothing about the timing of his research in any way affects its reliability.

Dr. Jeske's age at the time he wrote his thesis is in no way relevant to a Rule 702 analysis, and the suggestion inherent in defendants' brief that his age in some way undermines his opinion is not well-taken: after all, Einstein developed his theory of relativity as a 26-year-old patent clerk.

This case would be completely beyond the ken of ordinary lay persons (myself included) without the help of scientists and physicians. I will not exclude evidence that will "assist the trier of fact to understand the evidence or to determine a fact in issue." Fed. R. Evid. 702.

c. Dr. Kiss

Hematologist/oncologist Dr. Joseph E. Kiss has been a professor of medicine and licensed physician for almost thirty years. He is board certified in internal medicine, hematology, oncology and transfusion medicine. Dr. Kiss is an associate professor of medicine at the University of Pittsburgh in the division of hematology and oncology, where he specializes primarily in benign hematology. He serves as medical director for the Central Blood Bank in Pittsburgh, the hemapheresis program at the University of Pittsburgh Medical Center and several surrounding hospitals, and the hematopoietic stem cell laboratory at the University of Pittsburgh. Dr. Kiss receives substantial funding from the National Institutes of Health (NIH), and is actively involved in research, teaching and patient care.

It is Dr. Kiss' opinion that the administration of contaminated heparin to patients resulted in a series of adverse events, including inflammatory and anaphylactic reactions, HIT, increased clotting, and increased bleeding. His opinions are based on his clinical and research experience, and published research studies of contaminated heparin, including animal studies, *in vitro* studies, clinical reports, and case series or adverse event reports.

Following the *Daubert* hearing held in April, 2011, the defendants withdrew their objections to the qualifications of Dr. Kiss. As Dr. Kiss demonstrated in the *Daubert* hearing, he is not only eminently qualified to offer his opinions, but those opinions are based on sound science.

Defendants nevertheless object to his testimony because: 1) he does not present any epidemiologic studies demonstrating a statistically increased incidence of HIT, bleeding or clotting; and 2) they view his use of "may" and "some" as indicating his opinions are expressed as possibilities instead of being within a reasonable degree of medical and scientific certainty.

I need not address again defendant's refrain that epidemiological evidence is required for an opinion to have a reliable basis. And the fact that an expert "does not use absolute terms but rather couches the opinions in terms of 'can' or 'may' does not render it speculative or unreliable." *In re Trasylol Prods. Liab. Litig.*, 2010 WL 1489730, *8 (S.D. Fla.).

d. Dr. Charles R. Buncher

Dr. Buncher is an epidemiologist and biostatistician with experience within the pharmaceutical industry. He has a bachelor's degree in biostatistics and epidemiology from the Massachusetts Institute of Technology and master's and doctorate degrees from Harvard University. Dr. Buncher has been a Professor of Biostatistics and Epidemiology in the Department of Environmental Health at the University of Cincinnati College of Medicine since 1973. He previously served as the Director of Graduate Training in the Department of Environmental Health from 2000 to 2010.

Dr. Buncher's opinions concern the contamination "epidemic" involving heparin, general principles of epidemiology, the CDC Blossom study, and the increased incidence of HIT as a result of exposure to OSCS contaminated heparin. He concludes that the Blossom study employed standard methodology, complied with accepted principles in the field of epidemiology and demonstrated a definitive causal relationship between the adverse events reported and contaminated heparin. He also summarizes published findings with regard to the association of HIT to contaminated heparin and

opines that the scientific evidence confirms the mechanism for activation of HIT antibodies by OSCS.

Defendants do not challenge Dr. Buncher's qualifications or the reliability of his opinions,[36] but appear to challenge his testimony on relevance grounds. As defendants point out, it does not appear that Dr. Buncher intends to opine as to general causation, but rather to offer his opinion as an epidemiologist and biostatistician as to the methodologies and merit of various studies cited by the parties in this dispute. Particularly given defendants' criticisms of these studies, which form the basis for many of the opinions of plaintiff's experts, this is information that would be helpful to the jury in weighing the evidence. As such, it is relevant.

e. Dr. Robert G. Luke

Dr. Luke is an internist and nephrologist with four decades of experience in the care and supervision of dialysis patients. He has served as the President of the American Society of Nephrology and as an adviser to the NIH. He has consulted with NIH clinical trials regarding treatment of progressive renal disease and end stage renal disease. He is a professor at the University of Cincinnati Medical Center.

Dr. Luke has served as a reviewer and editor for numerous scientific journals, including the New England Journal of Medicine. Dr. Luke has published extensively within his field, including scientific articles, abstracts, books, and book chapters, and has given numerous presentations.

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[36] Defendants argue that because Dr. Buncher addresses the same HIT studies as Drs. Hoppensteadt, Jeske and Kiss, any causation opinion on HIT he may offer should be excluded as unsupported. I disagree. As discussed at length above, the studies on HIT alone do not meet legal standards for reliability. But as Dr. Buncher explained in deposition, "I think what we have now established is any study by itself is insufficient to prove cause. Obviously, therefore, the question is what happens when we put them all together." Buncher Dep. at 57; [Doc. 528-2, at 4].

Dr. Luke's opinions concern injuries caused by contaminated heparin to hemodialysis patients. Dr. Luke intends to testify that the adverse events linked to exposure of contaminated heparin can be explained by virtue of activation of the blood contact, complement, and/or coagulation system.

Dr. Luke adopts and endorses the opinions set forth by the Kishimoto, Adiguzel and Blossom studies, among others. He also notes that the observations from the Kishimoto study involving pigs are consistent with observations of patients receiving contaminated heparin. Adverse reactions stemming from activation of the blood contact, complement and/or coagulation systems, he states, are neither typical nor expected in patients undergoing dialysis with uncontaminated heparin. It is his opinion that contaminated heparin led to an increased rate of HIT.

i. Qualifications

Defendants challenge Dr. Luke's qualifications to testify regarding HIT, arguing that such testimony exceeds his expertise. Plaintiffs do not address these challenges to Dr. Luke's qualifications, noting incorrectly that "[d]efendants do not challenge the qualifications of Drs. Luke or Buncher." [Doc. 549, at 161 n. 364]. I nevertheless have sufficient information in Dr. Luke's curriculum vitae, deposition and expert report to determine the adequacy of his qualifications. It is plaintiffs' burden of proof, but where there is evidence I may consider, I will not set aside my duty to weigh the evidence on the basis of poor briefing.

An expert may not testify beyond the scope of his or her expertise, and holding a medical degree "is not enough to qualify [a doctor] to give an opinion on every conceivable medical question." *Christophersen v. Allied-Signal Corp.*, 939 F.2d 1106, 1113 (5th Cir. 1991). But a doctor need not be a specialist in the exact area of medicine implicated by the plaintiff's injury." *McCullock*

v. H.B. Fuller Co., 61 F.3d 1038, 1043 (2d Cir. 1995). So long as the expert has some specialized knowledge as a result of training or experience relevant to the opinions he offers, his testimony will meet the qualification requirement.

As a practicing nephrologist who treats dialysis patients, Dr. Luke has experience identifying adverse events such as HIT and is qualified to testify about such adverse events. He is unquestionably qualified to testify regarding typical and atypical adverse events occurring during and after hemodialysis.

As to the contact, complement and coagulation systems, Dr. Luke testified in deposition that "ace inhibitors are very important drugs for nephrologists and cardiologists, and I know about angioedema and bradykinin and things like that. . . . I do have a fair background in renal physiology, and bradykinin is produced by the kidney as well as other areas. And it does have some effects on renal blood flow and things like that." Luke Dep. at 157. While Dr. Luke may not have the level of expertise that a hematologist would have, he does have "special knowledge" on these systems sufficient to qualify him as an expert.

ii. Reliability

Defendants argue, as they did with Drs. Hoppensteadt, Jeske, Kiss and Buncher, that Dr. Luke's opinion that contaminated heparin can cause HIT "is entirely unsupported by scientific evidence." [Doc. 528-1, at 69]. Again, defendants equate a lack of a study of statistical significance with a lack of evidence, and again conflate admissibility and sufficiency. I need not again explain my disagreement with defendants.

I find Dr. Luke's opinions to be based on reliable methodology and relevant.

f. Dr. Joseph S. Ohr

Dr. Ohr is a physician and surgeon licensed in Ohio and Illinois. He is a board certified forensic pathologist, anatomical pathologist and registered pharmacist. He is the deputy coroner and attending forensic pathologist at the Mahoning County Coroner's Office in Youngstown, Ohio. As such, he investigates sudden and unexpected deaths and attempts to determine, among other inquiries, the manner and cause of death. He conducts autopsies, takes cultures of body fluids and organs, and analyzes pathology results, toxicology screening, x-rays and laboratory tests. As a board certified pharmacist, he has particular knowledge and expertise in the biological effects of pharmaceutical drugs.

Dr. Ohr's opinions are based upon his review of seventy published studies and Dr. Jeske's expert report. He concludes that contaminated heparin activates the blood contact, complement and coagulation systems. In addition, he opines that injection of contaminated heparin more likely than not causes or contributes to sepsis or a septic-like response in patients with end-stage renal disease.

Dr. Ohr's list of credentials is impressive. But defendants state that plaintiffs have failed to make Dr. Ohr available for deposition, and in fairness to defendants, I cannot permit his testimony unless they have had the opportunity to depose him. Plaintiffs shall make Dr. Ohr available on or before September 1, 2011, or such date shortly thereafter as shall be agreeable to counsel and Dr. Ohr, or he shall not be permitted to testify.

2. Defendants' Evidence

a. Dr. Ronald Burch

Dr. Burch is the chief medical officer of Naurex Pharmaceuticals, Inc. Defendants represent him as an adjunct professor of bioengineering at Northwestern University School of Engineering,

although Dr. Burch has not yet been formally offered this position. Dr. Burch received his Ph.D. in pharmacology from the Medical University of South Carolina in 1981. He received his M.D. from the same institution in 1985. As a doctoral student, he worked on signal transduction in regulation of the coagulation, complement and fibrinolytic systems and their role in the inflammatory processes.

Following his degree, Dr. Burch served as a medical staff fellow at the National Institute of General Medical Sciences until 1987. He continued as a guest researcher at the National Institute of Mental Health from 1987 to 1991.

In 1987, Dr. Burch joined Nova Pharmaceutical Corp., and spent his first year there as a staff scientist on the bradykinin project, studying the biology of bradykinin and the pharmacology of antagonists of the bradykinin receptor.

Since 1992, Dr. Burch has worked with a number of pharmaceutical companies and start-ups, supervising research, writing safety protocols, leading development teams and clinical development, and communicating safety information to the FDA.

Dr. Burch has authored or co-authored over 200 published articles. He published many articles on bradykinin in the 1980s and 90s. He authored the chapter on bradykinin receptors in the Encyclopedia of Biological Chemistry in 2004.

Dr. Burch has offered expert medical causation testimony in more than twenty cases.

Dr. Burch offers opinions on both general and specific causation. It is his opinion that the administration of contaminated heparin resulted in acute inflammatory reaction, and that anaphylaxis should be ruled out. Dr. Burch opines that the McKee study confirms that bradykinin is the sole mechanism responsible for the signs and symptoms resulting from the administration of

contaminated heparin, and that any complement activation was a minor accompaniment of the activation of the contact system. Dr. Burch concludes that the effects of contaminated heparin are therefore immediate, transient and non-serious.

Dr. Burch also critiques the opinions of plaintiffs' experts, asserting that they are inconsistent with the mechanism of action he identifies. He also asserts that there is no evidence that contamination increases the risk of death, adverse events more than a few minutes after administration, bleeding or clotting, HIT or sepsis. He states in his report that "the fact that plaintiffs' experts expressed the opinion that OSCS contamination could lead to a spectrum of adverse events completely at odds with the mechanism of action discussed above confirms that their methodology is flawed and not valid." [Doc. 457-1, at 17]. He also opines that "properly conducted studies in human beings must be undertaken to determine whether an agent can cause disease in humans." *Id.*

i. Qualifications

Plaintiffs argue that Dr. Burch is not qualified to give opinions as to the biological effects of contaminated heparin. While acknowledging Dr. Burch's education and his experience with bradykinin, plaintiffs point out that the vast majority of Dr. Burch's work with the peptide was almost twenty years ago. His only experience treating patients occurred in medical school, nearly thirty years ago. Dr. Burch's professional focus for the last decade has been of a supervisory and regulatory nature. Plaintiffs point out that his expertise is on bradykinin, a single peptide, and that he has never studied heparin or contaminated heparin. They claim he is therefore not qualified to give an opinion on reactions to contaminated heparin.

Plaintiffs argue that as Dr. Burch prepared his opinions solely for litigation purposes, his opinions are suspect and should be subjected to more rigorous scrutiny. The Sixth Circuit has held that "if a proposed expert is a 'quintessential expert for hire,' then it seems well within a trial judge's discretion to apply the *Daubert* factors with greater rigor." *Johnson v. Manitowoc Boom Trucks, Inc.*, 484 F.3d 426, 435 (6th Cir. 2007).

Defendants reject plaintiffs' contention that Dr. Burch prepared his testimony solely for litigation purposes. They note that he relies on his own research on bradykinin and state that his expert report "is meticulously supported with citations to scientific literature, published completely independent of this litigation."[Doc. 457, at 16].

Although defendants are correct that Dr. Burch's report is replete with citations to scientific literature, he relies most heavily on the McKee study in reaching his opinions. *See* [Doc. 457-1]. Moreover, it is undeniable that the last twenty years of his career have been largely dedicated to consulting, including serving as an expert witness.

Dr. Burch certainly has extensive knowledge about bradykinin, even if he acquired his expertise many years ago. The lynchpin of Dr. Burch's proffered testimony is that bradykinin is the mechanism of the adverse reactions. Most of his other opinions flow from this conclusion. Plaintiffs' concern about the limited nature of his expertise is understandable—when all you have is a hammer, everything becomes a nail. But "the application of the *Daubert* factors is germane to evaluating whether the expert is a hired gun or a person whose opinion in the courtroom will withstand the same scrutiny that it would among his professional peers." *Watkins v. Telsmith, Inc.*, 121 F.3d 984, 991 (5th Cir. 1997). Defendants have shown that Dr. Burch has sufficient qualifications to form these opinions.

Dr. Burch, however, offers testimony beyond his expertise.

There is no indication that Dr. Burch has any specialized knowledge relating to thrombin formation or heparin-induced thrombocytopenia. He may not, therefore, offer opinions on these subjects nor critiques of the opinions of plaintiffs' experts on these subjects.

Nor may Dr. Burch offer opinions on specific causation. Dr. Burch may have a medical degree, but he has never treated patients except under the supervision of a licensed physician during his medical school training thirty years ago. His opinions on specific causation do not derive from differential diagnosis or a consideration of the patients' medical histories. He simply observes that the injuries do not match his causation theory and then concludes that contaminated heparin is not responsible.

ii. Reliability

Plaintiffs claim that Dr. Burch's knowledge of a single peptide, bradykinin, is an insufficient basis for his opinions, which contradict undisputed scientific literature. They argue, therefore, that his opinions lack any reliable scientific basis.

As discussed above, Dr. Burch has at best limited experience with heparin, and has never studied heparin or contaminated heparin. But Dr. Burch nevertheless stated that he relied solely on experience to make his final decisions. He testified that he did not believe that any of the articles he cited were authoritative, that he used the published literature "as examples that either agree with my opinion or don't agree with my opinion." Burch Dep. at 26, 152. Because Dr. Burch's opinions are untested and not peer-reviewed, he must supply scientific and medical evidence supporting his theories.

It is Dr. Burch's opinion that because there is no evidence for an immune response mediated by IgE (an antigen complex) to contaminated heparin, anaphylaxis is not responsible for the constellation of symptoms including facial edema, tachycardia, hypotension, urticaria and nausea. He cites a single study to support this finding, Mike Martin, *et al.*, *Analysis of Cytokine Secretion from Lymphocytes of Patients with Hypersensitivity Reactions to Contaminated Heparins*, 164 British J. of Dermatology 68 (2011).

Martin *et al.* reported the results of an *in vitro* study on cytokine secretion. After comparing the secretion of cytokines of individuals with and without hypersensitivity to heparin, the authors concluded that "the *in vitro* lymphocyte reactivity pattern of peripheral blood mononuclear cells from individuals with hypersensitivity reactions to contaminated heparins was neither typical for an immune-mediated nor for a nonimmune-mediated reaction." They found that "truly allergic, immune-mediated hypersensitivity to a heparin exhibited *in vitro* findings different from those of the suspected non-immune mediated hypersensitivity to OSCS-contaminated heparins." They also noted that "possible effects of heparins in the test system itself may require consideration."

For his opinion that anaphylaxis may be ruled out, Dr. Burch thus relies entirely on one study, whose authors were not confidant in their results. Dr. Burch has not shown any special knowledge of anaphylaxis or other allergic-type reactions. The reliability of this opinion is questionable. Nevertheless, he relies on a published, peer-reviewed study in reaching it, and the weaknesses therefore more properly go to weight rather than admissibility.

Dr. Burch also opines that an anaphylactoid reaction can be ruled out, an opinion he bases on the McKee study. The McKee study reported finding no evidence that OSCS contaminant activated basophils, monocytes or neutrophils. Based on this, McKee *et al.* concluded that kallikrein

activation is the sole pathway for bradykinin production. The McKee study did not provide its data for this investigation.

As noted, plaintiffs' experts disagree with the methodology employed by the McKee study and the conclusions the authors reached. As I discussed above, the fact that experts disagree does not render their testimony unreliable.

Dr. Burch's opinions regarding bradykinin, its activation, and its acute, self-limited pathophysiological effects are based on Dr. Burch's expertise and the peer-reviewed, published McKee study. His testimony on these biological mechanisms appears sufficiently reliable to go before a jury.

Dr. Burch's responses to plaintiffs' experts are more problematic.

Dr. Burch offers several opinions as to the methodology employed by plaintiffs' experts. Dr. Burch is not qualified to testify as to specific causation or HIT, and so his critiques of plaintiffs' experts on these subjects are not admissible.

Many of Dr. Burch's opinions critiquing Dr. Hoppensteadt's opinions will not be helpful to the jury, as I have excluded her opinions as to sepsis and symptoms occurring after sixty minutes of heparin administration. Dr. Burch also opines that Dr. Hoppensteadt's conclusions are incorrect because she fails to consider the natural inhibitors of the feedback loops she describes. But Dr. Burch admitted at the *Daubert* hearings that a patient's pathophysiology and co-morbidities can affect the presence of these inhibitors in the blood. He also admitted that he was unfamiliar with patients in a dialysis setting.

Dr. Burch's failure to consider the vulnerabilities of the patient population weakens his opinion. But it does not render his opinion "junk science," and the knowledge of how these

biological mechanisms behave in a healthy human being may be of some assistance to the fact finder. "Vigorous cross-examination, presentation of contrary evidence, and careful instruction on the burden of proof are the traditional and appropriate means of attacking shaky but admissible evidence." *Daubert*, *supra*, 509 U.S. at 597.

Dr. Burch states in his report that "the CDC case definition was intentionally overly broad in order to capture all possible patients who experienced adverse events." Burch Rpt. at 17. This opinion misrepresents the CDC case definition. The CDC case definition was "intentionally broad to accommodate the many presentations and potential sources of allergic-type reactions in the absence of a clear cause or mechanism."[37] The point of the definition, therefore, was not to identify all adverse events, but to identify the source or cause of the identifiable adverse events. Blossom *et al.* noted that "it was difficult to build precise case definitions owing to inherent uncertainties in this investigation." They cautioned "some true cases may have been misclassified as noncases."[38] Dr. Burch's opinion as to the CDC definition is unreliable and shall be excluded.

Dr. Burch also opines that the fact that plaintiffs' experts expressed opinions at odds with the mechanism of action he identifies "confirms that their methodology is flawed and not valid." Burch Rpt. at 17. Although an expert may critique the methods of another expert, this opinion strays into a legal conclusion. "An expert opinion on a question of law is inadmissible." *Chavez v. Carranza*, 559 F.3d 486, 498 (6th Cir. 2009) (quoting *Berry v. Detroit*, 25 F.3d 1342, 1353–54 (6th Cir. 1994)). Dr. Burch's conclusion that "properly conducted studies in human beings must be undertaken to determine whether an agent can cause disease in humans" is likewise inadmissible.

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[37] Blossom, *supra* note 1, at 2682.

[38] *Id.* at 2683.

Dr. Burch's testimony as to bradykinin and its effects is admissible. I note, however, that Dr. Burch misrepresented his qualifications before this court (and others). These misrepresentations do not affect the substance of his testimony, and as I believe defendants were unaware of these falsehoods, I will not exclude Dr. Burch's testimony for this reason. I will, however, provide a cautionary instruction informing the jury that Dr. Burch lied under oath in this proceeding and others about some aspects of his credentials, and his opinions are therefore subject to greater scrutiny.

b. Dr. Joseph Ory

Dr. Ory is an epidemiologist and medical doctor with a long and distinguished career in the public health field. He is a fellow of the American College of Preventive Medicine, a fellow of the American College of Epidemiology, a member of the American Epidemiology Society, a member of the Society of Epidemiological Research and a member of the American Public Health Association. He is licensed to practice medicine in Georgia and is board certified in preventive medicine.

Dr. Ory spent approximately twenty-three years working for the CDC. From 1994 to 1996, he served as Vice President and Senior Scientist at the Prudential Center for Health Care Research, and is now a private consultant. He has served as a member of, and consultant to, committees of the World Health Organization, the FDA and the CDC.

Dr. Ory has written extensively on epidemiological and medical issues, authoring or co-authoring over 100 articles in the medical literature.

Dr. Ory offers a range of opinions regarding the claims in this proceeding. Dr. Ory describes the basic epidemiological approach to determination of causality, reviews the CDC investigation and

findings and other studies, and analyzes the plaintiffs' scientific evidence relating to the alleged adverse effects from contaminated heparin.

Dr. Ory observes that the various diseases and conditions at issue in these proceedings occur commonly in patients receiving heparin in the absence of any contamination. Accordingly, based on his review of the medical literature, Dr. Ory states that the studies on which plaintiffs' experts rely do not provide a sufficient foundation to conclude that contaminated heparin causes any of the symptoms not defined by the CDC study. Essentially, Dr. Ory's opinion is that without an epidemiological study, a scientist cannot validly draw a causal relationship where the conditions occur regularly among patients without exposure to contaminated heparin.

Plaintiffs do not challenge Dr. Ory's qualifications or his descriptions of the epidemiological method. They claim, however, that Dr. Ory impermissibly opines on the law when he states that epidemiologic evidence is necessary to establish causation.

I fully appreciate plaintiffs' concern that Dr. Ory's opinion may prove misleading to a jury. But I find that plaintiffs' contention that Dr. Ory impermissibly offers a legal conclusion to be overstated.

Dr. Ory does not assert that the only means of proving a scientific fact is epidemiology. He states that, given the fact that the conditions allegedly caused by contaminated heparin also occur in patients not exposed to contamination, he believes epidemiology is the only way to generate a reliable opinion on causation in this case.

Dr. Ory criticizes the methods of plaintiffs' experts and disagrees with their conclusions, but this criticism in no way invades my authority on admissibility. Opposing experts may—and usually

do—disagree with regards to methodology and conclusions. Their critiques of each others methods are helpful to the jury, which must determine the weight to accord each expert's testimony.

Dr. Ory may not testify that plaintiffs must present epidemiological evidence to establish legal causation in this case, as instructing the jury is the province of the court. Testimony of an expert that constitutes mere personal belief as to the weight of the evidence invades the province of the jury. *McGowan v. Cooper Indus., Inc.*, 863 F.2d 1266, 1273 (6th Cir. 1987); *STX, Inc. v. Brine, Inc.*, 37 F. Supp. 2d 740, 768 (D. Md. 1999) (quotation omitted); *Sec. & Exch. Comm'n v. Lipson*, 46 F. Supp. 2d 758, 763 (N.D. Ill. 1998).

But I will not prevent him from testifying about the various methodologies used by plaintiffs' experts, or from giving his opinions about medical causation. Any risk of confusion will be cured by the traditional tools of advocacy: "[v]igorous cross-examination, presentation of contrary evidence, and careful instruction on the burden of proof." *Daubert*, *supra*, 509 U.S. at 597.

B. Summary Judgment

Having determined the admissibility of the parties' experts and their opinions, I now turn to the issue of summary judgment on the claims identified by defendants. The fact that an expert's opinion is admissible under Rule 702 does not necessarily mean it is adequate to defeat a motion for summary judgment. *Daubert*, *supra*, 509 U.S. at 596. I must determine, for each category of claims, whether there is sufficient evidence that a reasonable juror could find that contaminated heparin is capable of causing the condition.

1. Symptoms Occurring More Than Sixty Minutes After Administration

Defendants argue that there is no scientific evidence that any clinical symptoms in either animals or humans occurred more than sixty minutes after administration of contaminated heparin.

They claim that the reported findings on this issue establish that the adverse events occurred, *and resolved*, well within the sixty minute time window in the CDC case definition. Plaintiffs counter that defendants mischaracterize the findings of these studies, and that they in fact lend support to their experts' causation opinions about the onset and duration of symptoms.

Plaintiffs' experts offered testimony regarding the onset of symptoms after sixty minutes, relying solely on the fact that Kishimoto study observed that kallikrein activity continued to increase during the sixty minute observational period. The testimony of plaintiffs experts on this point does not meet the requirements of Rule 702. There is "simply too great an analytical gap between the data and the opinion[s] proffered." *Gen. Elec. Co. v. Joiner,* 522 U.S. 136, 146 (1997). Again, I note that, though plaintiffs' experts offer plausible testimony, plausibility is not the standard. "The courtroom is not the place for scientific guesswork, even of the inspired sort. Law lags science; it does not lead it." *Rosen v. Ciba-Geigy Corp.*, 78 F.3d 316, 319 (7th Cir. 1996).

It is plaintiffs' burden to produce credible, scientific evidence demonstrating a genuine issue of material fact as to general causation. Plaintiffs have not met this burden regarding the onset of symptoms after sixty minutes. Summary judgment is therefore appropriate as to these claims.

This judgment does not, however, include any plaintiff claiming symptoms or continuing adverse effects proximately caused by the contaminated heparin or its effects continuing beyond the sixty minute time-frame. As plaintiffs' experts note, the Blossom study indicates that in roughly twenty-four percent of cases reported, the patients required either further evaluation in the emergency room or hospitalization due to symptoms persisting. Plaintiffs' experts also rely on a case study contained in the Kishimoto study in which a patient experienced a sudden drop in blood

pressure after administration of Baxter heparin, continued to feel ill after dialysis and ultimately remained in the hospital for two days.

My ruling restricting claims to those in which one or more symptoms were apparent within the sixty minute period does not include claims of HIT. Plaintiffs have submitted sufficient admissible proof that HIT, unlike other alleged symptoms attributable to contaminated heparin such as bleeding, clotting and effects identified by the Blossom and McMahon studies, develops over time.

2. HIT

Defendants argue that there is no scientific study or data demonstrating that contaminated heparin more likely than not causes HIT. They point out that HIT is a potential side effect of uncontaminated heparin, and in the absence of epidemiological evidence showing an increase in the incidence of HIT among patients exposed to contaminated heparin, plaintiffs have not sufficiently proved that contaminated heparin caused HIT.

Epidemiological evidence is undoubtedly a reliable indicator of general causation, but plaintiffs have produced credible scientific evidence that contaminated heparin can increase the risk of HIT. Construing all the evidence in the light most favorable to the plaintiffs, I find that the evidence they put forth through their experts creates a genuine issue of material fact, such that summary judgment is inappropriate.

3. Sepsis and Sepsis-Like Responses

Because I have excluded Dr. Hoppensteadt's testimony on sepsis, plaintiffs' only remaining expert on the subject is Dr. Ohr. Pending completion of his deposition, and further briefing (to be

scheduled at the next status/scheduling conference), I hold consideration of defendants' summary judgment motion as to this issue in abeyance.

4. Bleeding or Clotting

Plaintiffs have submitted reliable expert testimony that contaminated heparin can cause bleeding and clotting complications. Relying on adverse event reports and published studies, Drs. Hoppensteadt, Jeske and Kiss opine that contaminated heparin can have stronger anticoagulant and bleeding effects than uncontaminated heparin.

While again, this evidence may not be as persuasive as an epidemiological study, defendants have not produced evidence showing these conclusions to be incorrect, and, as discussed above, the plaintiffs' experts meet the standards for admitting their testimony.

Plaintiffs have shown that there is a genuine issue of material fact, and summary judgment as to these claims is therefore denied.

5. Injury Resulting from Non-Bolus Doses

Plaintiffs have put forth no reliable evidence of injuries resulting from non-bolus doses. Though there is evidence that contaminated heparin can cause a variety of adverse events, defendants are correct that the epidemiological studies indicate bolus doses, rather than other routes and dose amounts, as being associated with adverse events.

Having found the testimony of Dr. Hoppensteadt on subcutaneous dosage unreliable, I cannot accept plaintiffs' argument that the FDA recalls of all contaminated products indicates that non-bolus doses can cause injury. Plaintiffs bear the burden of proof, and they have not met that burden for these claims.

6. Injuries Caused by Contaminated Heparin Containing Less Than 15% OSCS

Defendants argue that there is no scientific evidence demonstrating that contaminated heparin containing less than 15% OSCS caused injuries or disease.

Although I have found that Dr. Hoppensteadt's opinion that there is *no* dose response is unreliable, this does not, in itself, mandate a ruling in favor of defendants on this claim. Defendants must first show the absence of a genuine issue of material fact before the burden shifts to plaintiffs. It may be that lower concentrations of contaminant lowers the risk of an adverse reaction, but I find no justification for defendants' 15% cut-off.

Defendants cite various sources for their claim, including Dr. Hoppensteadt's letter to the editor,[39] the initial decision of European authorities not to recall heparin products containing OSCS concentrations of 5–7%, and Dr. Buncher's discussion of a rat study showing no adverse reactions in animals exposed to concentrations below 12–20%. But even assuming this evidence is reliable, it hardly shows that there is no issue of material fact that the threshold below which contaminated heparin has no effect is concentrations below 15%. Summary judgment is therefore inappropriate.

7. Diseases and Conditions Falling Outside the CDC Case Definition

The CDC case definition, as reported in the Blossom study, categorized a definite case as a sudden onset of angioedema or urticaria in a patient within one hour after the administration of heparin. It categorized a probable case as the development within one hour after initiation of hemodialysis of hypotension, loss of consciousness, or signs and symptoms from at least two of the

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[39] Jawed Fareed, *et al.*, *Contaminants in Heparins Continue to Be Unfolded*, 27 Int'l Angiology 457, 460 (2008). As discussed above, Dr. Hoppensteadt has changed her opinion in light of subsequent studies.

following three categories: burning sensation; warmth or flushing; numbness or tingling; difficulty swallowing; shortness of breath; audible wheezing or chest tightness; tachycardia; and nausea, vomiting or diarrhea.

As discussed above, I find that plaintiffs have presented credible evidence that contaminated heparin can cause certain diseases and conditions falling outside the CDC case definition. Summary judgment is therefore denied as to this catch-all category of claims.

Conclusion

For the foregoing reasons, it is hereby

ORDERED THAT:

1. Defendants' omnibus motion to exclude general causation testimony [Doc. 528] be, and the same hereby is granted in part and denied in part, and held in abeyance as to Dr. Ohr, as provided herein;
2. Defendants' omnibus motion for summary judgment [Doc. 527] be, and the same hereby is granted in part and denied in part, as provided herein;
3. Plaintiffs' motion to exclude the opinion testimony of Dr. Burch [Doc. 438] be, and the same hereby is granted in part and denied in part, as provided herein;
4. Plaintiffs' motion to exclude the testimony of Dr. Ory [Doc. 442] be, and the same hereby is denied; and
5. A status/scheduling conference shall be held Monday, August 22, 2011, at 1:30 p.m., EDT, subject to the availability of lead counsel, or at such other date and time within that or the following week as may be convenient for such counsel; counsel to submit the agenda(s) three calendar days before said conference.

So ordered.

/s/ James G. Carr
Sr. United States District Judge